T. HARSHA VARDHAN

Manipal Prep Manual of Medicine

Md. Jany baba.

Second Edition

Manthappa M
MBBS, MD (Internal Medicine)

Associate Professor
Department of Medicine
JSS Medical College, JSS University
Mysuru, Karnataka

Former Associate Professor, Department of Medicine
Kasturba Medical College, Manipal University
Manipal, Karnataka

Email: manthappa@yahoo.com

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Ph: 23289259, 23266861, 23266867 Fax: 011-23243014 Website: www.cbspd.com
e-mail: delhi@cbspd.com; cbspubs@airtelmail.in.
Corporate Office: 204 FIE, Industrial Area, Patparganj, Delhi 110 092
Ph: 4934 4934 Fax: 4934 4935 e-mail: publishing@cbspd.com; publicity@cbspd.com

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Contents

1 Infectious Diseases

Q. Define the terms infection, colonization, and infestation.

- ***Infection***: Invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms. Infection can be localized, as in pharyngitis, or widespread as in sepsis.
- ***Colonization***: It is the simple presence of potentially pathogenic microbes in or on a host.
- ***Infestation***: Refers to presence of parasites inside or on the host.

Q. Discuss the serological (immunological) methods used in the diagnosis of infectious diseases.

- Serological (immunological) methods involve detection of antigen or antibody of a microorganism in a given sample. These are as follows:
  - Enzyme-linked immunosorbent assay (ELISA)
  - Rapid immunochromatographic test
  - Western blot (immunoblot) test
  - Immunofluorescence test
  - Complement fixation test
  - Agglutination test
  - Immunodiffusion
  - Immunoelectrophoresis

Enzyme-linked Immunosorbent Assay (ELISA)

- ELISA or the enzyme immunoassay (EIA) makes use of enzyme-labeled immunoglobulin to detect antigens or antibodies. It is a sensitive and specific test for the detection and quantification of antigens or antibodies.
- ELISA tests are usually performed in microwell plates. Microwells in ELISA plates are coated with antibodies to the target proteins (antibodies or antigens). Clinical sample is added into these microwells. If a specific antigen or antibody is present in the clinical specimen, it is captured by the coated antibodies on the ELISA plate. A second antibody to the target protein conjugated with an enzyme is then added which is captured by the target protein. The unbound material is washed out. A chromogenic substrate (to the enzyme) is then added.

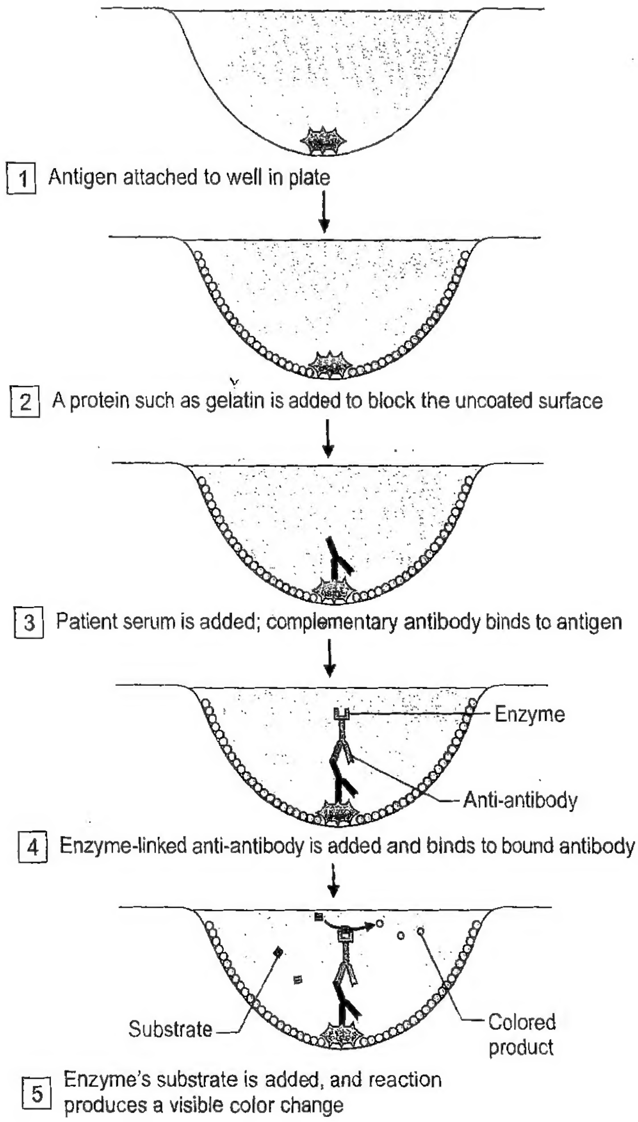

Fig. 1.1: ELISA

Development of color by the action of hydrolyzing enzyme on chromogenic substrate indicates the presence of the specific antigen or antibody. Color intensity is measured by the spectrophotometer.

- There are many variations of ELISA, but the basic principle remains the same as described above. In the first-generation ELISAs either crude antigen or single antigen is used for the test. In the second- and third-generation ELISAs multiple antigens or recombinant antigen or/and specific peptides are used, which improves the sensitivity and specificity of the test.
- ELISA is routinely used to detect antibodies against HIV and hepatitis A virus.

Rapid Immunochromatographic Test

- Here, the principle is same as ELISA, but the technique is embedded in a nitrocellulose membrane of a test strip. This allows rapid detection of antigen or antibodies in patient's body fluids such as blood or serum. The presence of specific proteins is indicated by the development of colored bands on the strip. These diagnostic strip tests are simple, rapid, cheap and reliable and can be used at home and clinics. Such kits have been developed for dengue, malaria, etc. Urine pregnancy test kit is also an example of immunochromatographic test which uses specific antibodies to selectively identify hCG in urine.

Western Blot (Immunoblot) Test

- In Western blot, antibodies to multiple specific proteins are detected. Hence, it has high specificity. Microbial protein is run on gel electrophoresis to separate the ligands, which are then transferred on to a nitrocellulose membrane strip. Patient's serum is added to this nitrocellulose strip. If there are antibodies to a specific microorganism, they bind to antigens present on the strip. Enzymatically labelled anti-immunoglobulins can be added now which bind to the antibodies and visualised by the addition of an enzyme substrate to produce colored bands. This test is commonly used to confirm the diagnosis of HIV infection.

Immunofluorescence Test

- This test makes use of immunoglobulin (antibody) labeled with fluorescent dye to detect antigens or antibodies. It requires a fluorescent microscope to read the signal. It is commonly used to detect infections with herpes virus, dengue virus and rabies virus.

Direct Immunofluorescence

- Direct immunofluorescence or direct fluorescent antibody (DFA) test uses a single antibody labeled with fluorescent dye to detect the presence of a specific antigen. If a specific antigen of a microorganism is present in patient's serum, it combines with the antibody labeled with a fluorescent dye which can be detected as a fluorescent signal. This test is highly sensitive and specific.

Indirect Immunofluorescence

- Here two antibodies are used. The first antibody recognizes the target antigen and binds to it, and the second antibody, which is labeled with a fluorescent dye recognises the first antibody and binds to it.
- This test is more complex than the direct immunofluorescence test and takes more time but allows more flexibility. Patient's serum is incubated with a specific microbial antigen. If specific antibodies are present in the patient serum, they combine with the antigen. Next, fluorescent-labeled antisera is added and the fluorescent signal is looked for.

Complement Fixation Test

- This test is used to detect presence of specific antibodies to a microorganism. It depends on the antigen–antibody reaction which uses complement. Patient's serum is heat treated to remove any free complement. It is then mixed with a specific antigen and sensitized sheep RBCs are added. Complement is added next. If antibodies are present in the patient's blood, there is formation of antigen–antibody complex and complement is used up. If there is no antibody, complement remains unused and it lyses the sensitized sheep RBCs. Absence of hemolysis means complement fixation test is positive which means that specific antibodies are present. This test has been largely superseded by other methods such as ELISA and PCR.

Agglutination Test

Direct Agglutination

- Here, the patient's serum is added to a known antigen. If antibodies are present in the patient's serum, it leads to agglutination. Weil-Felix test for scrub typhus and direct agglutination test (DAT) for visceral leishmaniasis are examples of this test.

Indirect (Passive) Agglutination Test

- Here, carrier particles such as RBCs, latex, or gelatin are coated with a soluble antigen and are mixed with patient's serum. These particles agglutinate if the patient's serum contains antibodies.
- In latex agglutination test, latex particles coated with specific antibody are mixed with patient's serum. If there

are specific antigens in the patient's serum, there is agglutination of antibody coated latex particles. This test is used to detect toxins of *Vibrio cholerae* and staphylococci.

- In hemagglutination test, RBCs are coated with known antigens. If mixed with serum containing specific antibodies, there is agglutination of RBCs. This is used in the diagnosis of syphilis and herpesvirus infections.

Immunodiffusion

- Immunodiffusion is a diagnostic test which involves diffusion through a substance such as agar gel. Here a specific antigen or antibody is placed in one well and patient's serum or body fluid is placed in another well and left for 48 hours. The antigen and antibody diffuse through the agarose gel towards each other and a precipitation line is formed between the two wells.

Immunoelectrophoresis

- Immunoelectrophoresis is a general name for a number of biochemical methods where proteins are separated by electrophoresis and identified using specific antibodies. This test is conducted on agarose gel. Four types of immunoelectrophoresis (IEP) have been used: electroimmunoassay (EIA also called rocket-immunoelectrophoresis), classical immunoelectrophoresis (IEP), immunofixation electrophoresis (IFE) and immunoprecipitation of proteins after capillary electrophoresis. The procedure used in most laboratories is immunofixation electrophoresis (IFE). IFE is widely used for identifying Bence Jones proteins seen in multiple myeloma.

Q. Discuss the molecular methods used in the diagnosis of infectious diseases.

- Molecular methods involve detection of RNA or DNA of a microorganism. These are polymerase chain reaction (PCR), southern blotting and northern blotting.

Polymerase Chain Reaction (PCR)

- This is the most specific and sensitive test of all molecular techniques. Here the nucleic acid sequence of a microorganism is amplified so that it becomes easily detectable. Since each microorganism has unique DNA/RNA sequences, it is possible to select a PCR primer that specifically identifies a particular microorganism.
- Multiple microorganisms can be identified in single clinical sample using 'multiplex' PCR.
- Fluorescent dyes can be attached to different primers and the final nucleic acid polymers examined by light spectroscopy.
- Reverse transcriptase (RT)-PCR amplifies very small amounts of any kind of RNA (mRNA, rRNA) and makes complementary DNA, which is then amplified with conventional PCR. HIV viral copies are estimated by this method.
- Real-time PCR is used to quantify the organisms and is used in estimation of HIV viral load.
- The disadvantages of PCR are its high cost and false positive results. False positive results happen if there is any contamination from laboratory or other sources.

Southern Blotting

- Southern blot is a method for detection of a specific DNA sequence in DNA samples. Southern blot is named for biologist Edwin Southern who developed this technique.
- DNA fragments are separated by gel electrophoresis and transferred on to a blotting paper. A DNA probe (this is a piece of single stranded DNA with known sequence labeled with a radioactive isotope or a fluorescent signal) is then added to the blotting paper. DNA probe will bind to its complementary DNA if present. This is then washed to remove any unbound DNA probe.
- Even after washing if there is radioactivity or fluorescence, it means that a specific DNA complementary to DNA probe is present. Since each microorganism has specific DNA sequences, it indicates the presence of that particular microorganism in the clinical specimen.

Northern Blotting

- This is same as Southern blotting except that RNA fragments are used here to detect microbial RNA instead of DNA.

Q. Define fever of unknown origin (FUO). Enumerate the causes of FUO. How do you approach a case of FUO?

Earlier Definition

- Fever of unknown origin (FUO) or pyrexia of unknown origin (PUO) is defined as fever of >38.3°C (>101°F) on several occasions for at least 3 weeks and failure to reach a diagnosis even after 1 week of inpatient investigation.

New Definition

As per new definition, FUO is classified into the following categories:

1. Classic FUO
2. Nosocomial FUO
3. Neutropenic FUO
4. FUO associated with HIV infection

- *Classic FUO* closely resembles the earlier definition of FUO. Classic FUO is defined as fever of ≥38.3°C (≥101°F) on several occasions which remains undiagnosed even after three outpatient visits or 3 days in the hospital or 1 week of "intelligent and invasive" ambulatory investigation.
- *Nosocomial FUO* is defined as a temperature of ≥38.3°C (≥101°F) on several occasions in a hospitalized patient in whom infection was not manifest or incubating at the time of admission which remains undiagnosed even after 3 days of investigation, including at least 2 days incubation of cultures.
- *Neutropenic FUO* is defined as a temperature of ≥38.3°C (≥101°F) on several occasions in a patient whose neutrophil count is <500/L or is expected to fall to that level in 1–2 days and remains undiagnosed after 3 days of investigation, including at least 2 days incubation of cultures.
- *HIV associated FUO* is defined as a temperature of ≥38.3°C (≥101°F) on several occasions over a period of >4 weeks for outpatients or >3 days for hospitalized patients with HIV infection which remains undiagnosed even after 3 days of investigation, including 2 days incubation of cultures.

Table 1.1 Causes of FUO

Infections (most common cause of FUO)

Bacterial
- Tuberculosis (very common cause of FUO)
- Typhoid
- Brucellosis
- Infective endocarditis
- Syphilis
- Melioidosis
- Sinusitis
- Osteomyelitis
- Prostatitis
- Dental abscesses
- Cholangitis
- Intraabdominal abscesses (subphrenic, renal, retroperitoneal, and paraspinal abscesses)

Viral
- HIV
- Chronic hepatitis (B,C, D)
- Infectious mononucleosis
- Q fever (*Coxiella burnetti*)

Parasitic
- Malaria
- Amebiasis
- Leishmaniasis
- Malaria
- Strongyloidiasis
- Toxocariasis
- Toxoplasmosis
- Trichinellosis
- Babesiosis

Rickettsial infections
- Q fever
- Rickettsialpox
- Rocky Mountain spotted fever
- Scrub typhus

Fungal
- Candidiasis
- Histoplasmosis
- Mucormycosis
- Blastomycosis
- Cryptococcal disease

Neoplasms (second most common cause of FUO)
- Lymphoma
- Leukemia and other hematologic malignancies
- Liver involvement with hepatoma or metastases
- Renal cell carcinoma
- Colon carcinoma
- Atrial myxoma

Inflammatory and connective tissue disorders
- Rheumatoid arthritis
- Systemic lupus erythematosus (SLE)
- Sarcoidosis
- Inflammatory bowel disease (IBD)
- Polyarteritis nodosa (PAN)
- Giant cell arteritis (common in elderly patients)
- Polymyalgia rheumatica
- Crohn's disease
- Granulomatous hepatitis
- Kikuchi disease

Miscellaneous
- Drug fever
- Factitious fever
- Periodic fever (familial Mediterranean fever)

Undiagnosed
- Even after extensive work up some FUOs may remain undiagnosed. Some of them may resolve spontaneously

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Approach to a Case of FUO

Clinical History

- Get a detailed history of general symptoms (e.g. fever, weight loss, night sweats, headache, rashes).
- Inquire about symptoms involving all major organ systems.
- Contact with infection (tuberculosis) or animals (cat scratch disease, brucellosis) or birds (psittacosis).
- High risk sexual behavior (HIV, hepatitis B).
- Travel history (suspect infections endemic in places visited).
- Drug therapy (suspect drug fever).
- Occupation (e.g. farmers prone for leptospirosis, veterinary workers prone for brucellosis).
- Recent dental treatment (possibility of endocarditis).
- H/O immunosuppression such as HIV infection or steroid therapy (suspect opportunistic infections).
- H/O previous abdominal surgery, trauma, endoscopy, or gynecologic procedures increase the likelihood of an occult intra-abdominal abscess.

Clinical Examination

- Do a complete physical examination.
- Document the height and pattern of fever. Measure the fever more than once and in the presence of a nurse to exclude factitious fever.
- Document BP, pulse, respiratory rate and SPO_2. BP may be low in septic shock and myocarditis. Pulse rate usually increases by 10 per degree celcius rise in temperature. Relative bradycardia (i.e. pulse rate does not correspond to the raise in temperature) may be seen in enteric fever, brucellosis and some viral infections. Relative tachycardia, i.e. pulse rate more than expected to the raise in temperature may be seen in myocarditis, sepsis, hypovolemia and thyrotoxicosis. High respiratory rate usually points to some respiratory pathology such as pneumonia, empyema, ARDS, etc.
- Look for lymphadenopathy (tuberculosis, infectious mononucleosis, HIV, lymphoma, malignancy), skin and mucosal lesions (skin rashes in connective tissue diseases, oral ulcers in Behçet's disease), pallor (may point to hematological malignancy, or a disseminated process such as TB involving bone marrow), jaundice (points to hepatobiliary disease), sternal tenderness (hematological malignancy), spinal tenderness (Pott's spine, epidural abscess), clubbing (TB, chronic suppurative lung disease) and for signs of meningeal irritation like neck stiffness and Kernig's sign (meningitis).
- Carefully examine heart for any murmurs (infective endocarditis), abdomen for any tenderness (deep abdominal infections) hepatosplenomegaly (enteric fever, malaria, hepatitis, hemolytic anemia) or splenomegaly (malaria, hematological malignancies).
- Always examine the fundus and retina (papilloedema in meningitis, retinal leisons in CMV infection, disseminated candidiasis, tuberculosis).

Investigations

- Common things are common. First try ro rule out common illnesses such as enteric fever, tuberculosis, malaria, UTI, HIV infection etc, and then only think of rare illnesses.
- Order routine investigations like Hb, total WBC count, RBC count, differential count, platelet count, ESR and peripheral smear study. Cytopenias may suggest a pathologic process involving bone marrow such as disseminated tuberculosis, hematological malignancies, etc. A high leucocyte count is common in infections. A very high leucocyte count may suggest leukemia. A very high ESR (>100 by Westergren method) often indicates active tuberculosis, collagen vascular disease or malignancy.
- Urine microscopy and culture sensitivity (to R/O UTI).
- If there is cough and sputum production, send it for Gram's stain, fungus stain, AFB, malignant cells and culture/sensitivity.
- Blood culture and sensitivity for both aerobic and anerobic organisms (infecting organism may be picked up by this).
- Complete LFT and RFT to look for any liver and renal involvement.
- Culture and examination of the stool for any ova, parasites and occult blood.
- Chest radiograph (tuberculosis, pneumonia, sarcoidosis).
- Mantoux test can help in diagnosing TB.
- ECG, echocardiogram (to look for signs of infective endocarditis).
- Ultrasound abdomen and pelvis to R/O any intra-abdominal pathology. Ultrasound can help in many ways. It can document any organomegaly, intra-abdominal lymphadenopathy or masses, ascites, any change in the texture of organs, any intra-abdominal collections of pus.
- Lumbar puncture and CSF examination if suspecting meningitis.
- Serological investigations (WIDAL test, ASO titre, HIV-ELISA, VDRL, TPHA, rheumatoid factor, antinuclear antibodies, viral antibody titres, Paul-Bunnell test, Brucella agglutination test).
- CT/MRI scanning (abdominal lymph glands, tumors, meningitis, abscesses).
- Tissue diagnosis (lymph node FNAC/biopsy, liver biopsy, bone marrow examination).
- Diagnostic surgical procedures like laparoscopy, exploratory laparotomy, etc may be required in undiagnosed cases.

Treatment

- Treatment depends on the underlying cause.
- Until a diagnosis is made, it is better to use only symptomatic treatment. Blind antibiotic therapy may make diagnosis of an occult infection more difficult, and empirical steroid therapy may mask an inflammatory response without treating the underlying cause.
- Sometimes when all the tests are negative and the cause of fever remains undiagnosed, a therapeutic trial may be indicated. For example, antituberculosis therapy (ATT) in suspected tuberculosis and steroid therapy in suspected connective tissue diseases.
- Periodic review is very important in cases of FUO as development of new signs and symptoms may help in identifying the underlying cause. In some cases a 'second opinion' by another physician can also be very helpful as different people think from different angles.
- Many undiagnosed cases of FUO will spontaneously resolve.

Table 1.2 Common situations where chemoprophylaxis is used

Situation	Goal	Chemoprophylaxis
Rheumatic fever	To prevent recurrence and further cardiac damage	Phenoxymethyl penicillin 250 mg twice daily or inj Benzathine penicillin once a month for many years as recommended
Meningitis • Due to meningococci • Due to *H. influenzae* type b	To prevent infection in close contacts	To reduce and prevent infection in close contacts and nasopharyngeal carriage Rifampicin 600 bd for 2 days Alternatives (single dose) ciprofloxacin 500 mg (po) or ceftriaxone 250 mg (iM) Rifampicin 600 mg daily for 4 days
Tuberculosis	To prevent infection in exposed tuberculin-negative individuals, infants of infected mothers and immunosuppressed patients	Oral isoniazid 300 mg daily for 6 months
Valvular heart disease Prosthetic heart valves	To prevent infective endocarditis	***Dental, oral, or upper respiratory tract procedures***: Amoxicillin, 2 g orally one hour before the procedure. If allergic to penicillin, azithromycin 500 mg can be used. ***Genitourinary or gastrointestinal procedures***: High-risk patients are given ampicillin (2 g intravenously or intramuscularly) plus gentamicin (1.5 mg/kg up to a maximum dose of 120 mg) 30 minutes before the procedure followed by ampicillin (1 g intravenously or intramuscularly) or amoxicillin (1 g orally) six hours later. Patients who are allergic to penicillin should receive the same dose of gentamicin plus vancomycin (1 g IV) one to two hours prior to the procedure.
Malaria	Prevention of malaria	Chloroquine one double strength tablet per week or mefloquine 250 mg once a week.
HIV infected patient with CD4 count below 200 cells/μl	Prevention of *Pneumocystis jiroveci* pneumonia	Trimethoprim-sulfamethoxazole, one double-strength tablet (960 mg) daily
HIV infected patient with toxoplasma IgG antibody positive and CD4+ T cell count <100/μl	Prevention of toxoplasmosis	Trimethoprim-sulfamethoxazole, one double-strength tablet (960 mg) daily
HIV infected patient with CD4 count below 50 cells/μl	Prevention of *Mycobacterium avium* complex infection	Azithromycin (1200 mg orally weekly) or clarithromycin (500 mg orally twice daily)

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Q. Chemoprophylaxis (Table 1.2).

- Chemoprophylaxis refers to the administration of a medication for the purpose of preventing an infection or disease.
- For example, antibiotics may be administered to immunosuppressed patients to prevent certain opportunistic infections. Antibiotics may also be given to healthy individuals to limit the spread of an epidemic, or to patients who have repeated infections (such as urinary tract infections) to prevent recurrence.

Q. Opportunistic infections (Table 1.3).

- Opportunistic infection is an infection by a micro-organism that normally does not cause disease, but becomes pathogenic when the body's immune system is impaired. Opportunistic infections are common in the following conditions:
  - Primary immune deficiency disorders
  - HIV infection
  - Steroid therapy
  - Chemotherapy for cancer
  - Immunosuppressing agents for organ transplant recipients
  - Malnutrition
  - Prolonged antibiotic therapy
- Opportunistic infections can be due to bacteria, viruses, protozoa or fungi.

Q. Nosocomial infections (hospital acquired infections).

- The term nosocomial infection or hospital acquired infection is applied to any clinical infection that was neither present nor was in its incubation period when the patient entered the hospital. Infections are considered nosocomial if they first appear 48 hours or more after hospital admission or within 30 days of discharge.
- They can manifest as *urinary tract infection, pneumonia, postoperative wound infection and other systemic infections*. Most common nosocomial infection is urinary tract infection.

Organisms

- ***Bacteria***: *Staphylococcus epidermidis* is the most common organism causing nosocomial infection. It most often causes wound infection. Other bacteria are *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* Acinetobacter, methicillin resistant *Staphylococcus aureus* (MRSA).
- ***Viruses:*** Hepatitis viruses (A, B, C), cytomegalovirus, influenza, respiratory syncytial virus, etc.
- ***Fungi:*** Candida, Aspergillus.
- ***Parasites:*** *Toxoplasma gondii, Pneumocystis carinii,* scabies.

Transmission

- Spread of nosocomial infection may occur through different routes.

Spread through Contact

- Contact with contaminated objects like bed pans, catheters, aspiration and suction equipment, dialysers, gloves, sponges, surgical instruments, etc. may lead to infection.

Table 1.3 Opportunistic infections

Organism	Disease	Treatment
Pneumocystis	Interstitial pneumonia	Sulphomethoxazole + trimethoprim.
Toxoplasma gondii	Encephalitis, myocarditis, pneumonia	Sulphadiazine + pyrimethamine. Alternative clindamycin
Cryptosporidium	Diarrhea	Spiramycin
Strongyloides	Diarrhea, episodes of septicaemia, pneumonia,	Thiabendazole
Herpes simplex virus	Encephalitis	Acyclovir
Varicella zoster virus	Disseminated herpes zoster	Acyclovir
Cytomegalovirus	Interstitial pneumonia, retinitis, meningo-encephalitis, gastrointestinal tract ulcers	Gancyclovir
Candida	Mucocutaneous, oesophageal, intestinal, endocarditis, systemic infection	Fluconazole, itraconazole, amphotericin-B
Cryptococcus	Disseminated infection, especially lung and meninges	Amphotericin-B + flucytosine

Spread through Vectors

- Salmonellosis and shigellosis may spread through flies, malaria may spread through mosquito.

Spread through Common Vehicle

- Patients may be infected after contact with a common vehicle, e.g. salmonellosis and hepatitis A may spread through infected food or water. Hepatitis B may spread through blood and blood products.

Airborne Spread

- This occurs by droplet nuclei and is seen in tuberculosis, chickenpox, and measles.

Prevention

- Nosocomial infections increase medical expenditure and also cause significant morbidity and mortality. Hence all efforts should be made to prevent them.
- Patients with infections should be isolated.
- Aseptic measures should be enforced in wards, operation theatres and labor rooms, by arranging clean air, clean linen, adequate airspace, etc. There should be adequate space between beds.
- Wound dressings and minor procedures like lumbar puncture, pleural and peritoneal tapping, etc. are better done in a separate procedure room and not bedside.
- Pharmacy should check all intravenous fluids before supplying to wards.
- The hospital kitchen staff should observe strict hygienic habits and should have periodic medical check up to detect and treat any infection.
- Every hospital should have an infection control committee which should monitor and control infections in the hospital.

Q. Food poisoning.

- Food poisoning is defined as an illness caused by the consumption of food or water contaminated with bacteria and/or their toxins, or with parasites, viruses, or chemicals. Green leafy vegetables are the most common cause of food poisoning, followed by dairy items and poultry.
- Food poisoning should be suspected when many people develop the illness after ingesting the same food and the illness bears a temporal relationship to food intake.

Table 1.4 Causes of food poisoning

Infective	Non-infective
Toxin mediated *Preformed toxin:* Staphylococcal enterotoxin, bacillus cereus *Toxin produced in the intestine:* Clostridial spp. *Vibrio cholerae*, enterotoxigenic *E. coli* ***Mucosal involvement*** Rotavirus, norwalk agent, shigella, giardiasis, *Campylobacter jejuni, Yersinia enterocolitica*.	Plant toxins (flava beans), paralytic shellfish toxin, ciguatera fish poisoning, scombotoxic fish poisoning, heavy metals (arsenic, thallium and cadmium)

Clinical features

- The commonest manifestation of food poisoning is a mixture of nausea, vomiting, fever, abdominal pain and diarrhea.
- Usually symptoms occur in many persons who ingest the same food.
- Symptoms usually develop within 48 hours after ingestion of food. In case of preformed toxins and noninfective food poisoning symptoms develop within minutes to hours.
- Specific etiologic agent can be identified by examining the suspected food, vomitus, stool or blood.

Management

- Most cases of food poisoning are self-limiting.
- Intravenous fluids and electrolytes should be given to patients with severe vomiting and diarrhea.
- Antidiarrheal agents (codeine phosphate, loperamide) can be used to control diarrhea. However, they should be avoided in young children, elderly, and patients who have fever and pain abdomen suggesting infective diarrhea.
- Antibiotics are not routinely indicated unless a specific pathogen is suspected.

Prevention of Food Poisoning

Following precautions can decrease the chances of food poisoning:

- Do not drink raw (unpasteurized) milk or foods that contain unpasteurized milk.
- Wash raw fruits and vegetables thoroughly before eating in running water.
- Use precooked, perishable, or ready-to-eat food as soon as possible.

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- Avoid cross contamination; keep raw meat, fish, and poultry separate from other foods.
- Thoroughly cook raw food from animal sources. Seafood and shellfish should be cooked thoroughly to minimize the risk of food poisoning.
- Refrigerate foods promptly. Never leave cooked foods at room temperature for more than two hours.

Q. Staphylococcal food poisoning.

- *Staph. aureus* is a common commensal of the anterior nares. *Staph. aureus* is coagulase positive and is the most virulent of all staphylococcal species. All other staphylococci have been collectively designated as coagulase negative staphylococci and are less virulent.
- Food handlers may transfer the bacteria via hands to foodstuffs such as dairy products, meats, eggs, and salads.
- After the food is left at room temperature, the organisms multiply and can produce a substantial quantity of heat stable enterotoxin.

Clinical Features

- Following ingestion of contaminated food, nausea, vomiting and abdominal cramps develop within 1–6 hours. Fever and/or diarrhea may also occur in a minority of patients.
- Most cases improve rapidly. Rarely severe dehydration can occur which can be fatal.

Management

- Fluid replacement and antiemetics (domperidone, ondansetron) should be given. Suspected food should be tested for the presence of enterotoxin and Staphylococcus if feasible. Public health authorities should be notified if food vending is involved.

Q. Toxic shock syndrome (TSS).

- Toxic shock syndrome (TSS) is a toxin-mediated acute life-threatening illness, usually caused by infection with either *Staphylococcus aureus* or group A *Streptococcus* (GAS, also called *Streptococcus pyogenes*).
- TSS was first described in a small group of children with acute febrile illness. Subsequently, it was found in young, menstruating women who were using a highly absorbent tampon that was newly introduced to the market. This was due to multiplication of vaginally colonized *S. aureus* and production of an exotoxin known as TSST-I and enterotoxin B. However, tampon associated cases of TSS have come down, and most cases are now secondary to *S. aureus* infections of skin or other sites.
- The criteria for the diagnosis of staphylococcal toxic shock syndrome are as follows:
  - Fever (usually >38.9°C or 102°F)
  - Diffuse macular rash, with desquamation 1–2 weeks after onset (including the palms and soles)
  - Hypotension (systolic blood pressure <90 mm Hg or orthostatic syncope)
  - Involvement of three or more of the following organ systems: Gastrointestinal (nausea and vomiting), muscular (myalgias), mucous membrane (hyperemia), renal, hepatic, hematologic (decreased platelets), central nervous system, or pulmonary (acute respiratory distress syndrome)
  - *Staph. aureus* infection or mucosal colonization
- TSS usually begins with nonspecific flulike symptoms such as fever and myalgia. In menstrual cases, the onset is usually 2 or 3 days after the start of menstruation. When the severity of illness increases, patients develop hypotension, erythematous rash and symptoms of multiple organ involvement such as vomiting, diarrhea, confusion, myalgias, and abdominal pain. Mucosal involvement is common (e.g. conjunctival hyperemia). Desquamation of the skin occurs during convalescence, usually 1–2 weeks after the onset of illness.

Investigations

- Investigations typically show leukocytosis, thrombocytopenia, increased urea, creatinine, hypoalbuminemia and liver function abnormalities.
- Gram staining and culture sensitivity of the infected specimen.
- Blood culture may show causative organism such as Staphylococcus or Streptococcus.

Treatment

- For staphylococcal toxic shock syndrome, large doses of a beta-lactamase-resistant, antistaphylococcal. antibiotic should be given intravenously. Antibiotic choices are nafcillin or oxacillin. Vancomycin can be used in penicillin-allergic patients. Clindamycin is also used in combination with above antibiotics for the first few days to reduce synthesis of TSST-1.
- For patients with group A *Streptococcus* infection, the drug of choice is clindamycin (600–900 mg IV q8h). Penicillin G (4 million U IV q4h) can also be combined with clindamycin for better effect.
- Duration of antibiotic treatment is 10 to 14 days.

Q. Enumerate the infections caused by streptococci. Write briefly on scarlet fever and erysipelas.

Streptococci are gram-positive bacteria arranged in chains. They cause a variety of infections in men which are as follows:
- Skin and soft tissue infections; cellulitis, erysipelas, necrotising fasciitis
- Bone and joint infections
- Tonsillitis
- Scarlet fever
- Glomerulonephritis
- Rheumatic fever
- Puerperal sepsis
- Endocarditis
- Urinary tract infection
- Neonatal infections including meningitis
- Female pelvic infections
- Peritonitis
- Dental infections
- Liver abscess.

Scarlet Fever

- Scarlet fever is a syndrome characterized by exudative pharyngitis, fever, and bright-red exanthem. Scarlet fever is caused by toxin producing group A beta-hemolytic streptococci (GABHS). GABHS is found in secretions and discharge from the nose, ears, throat, and skin.
- Exotoxin-mediated streptococcal infections range from localized skin infection (e.g. bullous impetigo) to the widespread eruption of scarlet fever to the highly lethal streptococcal toxic shock syndrome.

Clinical Features

- Scarlet fever is characterized by exudative pharyngitis, fever, and *scarlatiniform rash*. Initially patient develops fever, headache, vomiting and sore throat, followed within 24 hours by a punctate erythematous rash. Erythematous rash is caused by erythrogenic toxin.
- Initially, the exanthem is seen on the tongue which becomes bright red with prominent red papillae. This appearance is called *strawberry tongue*. The rash then appears on the neck and spreads to trunk and extremities. These rashes enlarge and join together to form a generalized erythema. Usually the rash does not affect nose, lips, palms and soles. Since the lips are not affected it remains pale and stands out against the red background of flushed cheeks. Rash is more prominent in the skin folds and is called *Pastia's lines*. Usually the rash becomes maximum by 2 days and fades by 7 days.

Differential Diagnosis

- Includes other causes of fever with generalized rash, such as:
  - Rubella, measles and other viral exanthems
  - Kawasaki disease
  - Toxic shock syndrome
  - Systemic allergic reactions (e.g. drug eruptions).

Complications

- Otitis media, pneumonia, septicemia, osteomyelitis, toxic shock syndrome, rheumatic fever, and acute glomerulonephritis.

Investigations

- Complete blood count. Leukocytosis is seen.
- Throat culture is the most important test to confirm the diagnosis.
- Direct antigen detecting kits allow immediate diagnosis but have less sensitivity.
- Anti-deoxyribonuclease B and antistreptolysin-O titers (antibodies to streptococcal extracellular products).

Treatment

- Penicillin is the drug of choice and is given for 7–10 days. Erythromycin is an alternative for patients allergic to penicillin.

Erysipelas

- It is an infection of skin and soft tissue.
- Erysipelas usually involves the face and head but other areas may also be involved.
- The skin becomes red, edematous and firm to hard in consistency due to cuticular lymphangitis. It may spread to adjacent parts and involve large areas. The margins of the erythematous areas are raised and sometimes vesicles are also seen. The patient may appear sick.
- Erysipelas of the face has to be differentiated from cellulitis. Since cellulitis is an infection of subcutaneous tissues, it does not involve the external ear which has no subcutaneous tissue, while facial erysipelas can involve external ear (Millian's sign).
- Penicillin is the drug of choice for erysipelas.

Q. Listeriosis.

- *Listeria monocytogenes* is an aerobic, gram-positive, rod. It is an intracellular organism and is capable of invading several cell types. Listeriosis is rare and occurs mainly in newborn infants, elderly patients, and immunocompromised patients.

Transmission

- Man gets infected through contact with infected animals such as rodents or ruminants, or by ingestion of

contaminated foods. The main route of acquisition of *Listeria* is through the ingestion of contaminated food products.

- Venereal transmission occurs occasionally.
- Perinatal infection causes still birth or a septicaemic illness in the newborn.

Clinical Features

- The disease is seen mainly in neonates and young children. Mother can get infected in late pregnancy which can lead to *still birth.* It presents as a febrile illness. The mother recovers after delivery but, occasionally, the organism persists in the genitalia to cause *habitual abortions*. If the neonate survives, the picture is one of severe infection. Neonates die in about three days but survivors develop suppurative meningitis.
- Listeria infection in healthy adults is uncommon but affects immunocompromised persons like AIDS patiens, diabetics, alcoholics and those with debilitating diseases. Listeria is an opportunistic infection in AIDS. *Meningitis* is often the clinical manifestation.

Investigations

- Organism can be isolated by blood culture, and culture of any infected body fluid such as CSF.

Treatment

- The response to treatment is slow.
- The *treatment of choice is intravenous ampicillin* often in combination with an aminoglycoside. Penicillin G can be used as an alternative to ampicillin.
- Trimethoprim-sulphamethoxazole is second line drug and can be used if the patient is allergic to ampicillin or penicillin.

Q. Discuss the etiology, pathogenesis, clinical features and complications of diphtheria. How do you investigate and manage a case of diphtheria?

Etiology

- Diphtheria is a localized infection of mucous membranes or skin that is caused by *Corynebacterium diphtheriae.* It is associated with a *characteristic pseudomembrane* at the site of infection.
- *C. diphtheriae* is a gram positive bacillus and resembles *Chinese letter patterns* on *Albert's stain.*
- There are 3 strains of *C. diphtheriae*; mitis, intermedius and gravis. Gravis causes the most severe disease.

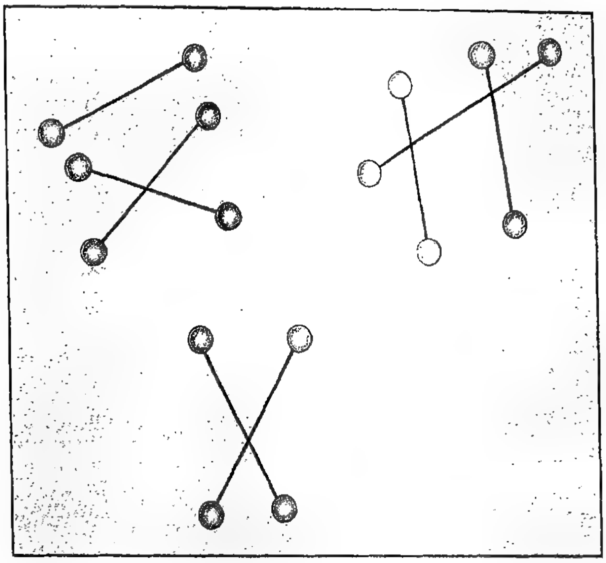

Fig. 1.2: Diphtheria bacilli

Epidemiology

- Diphtheria affects people all over the world. But now it is uncommon due to immunization practices. It is more common during winter. It is mainly a disease of children.
- Humans are the main reservoir of *C. diphtheriae*. However, some cases have also occurred due to transmission from livestock.
- Spread occurs in close-contact settings through respiratory droplets or by direct contact with respiratory secretions or skin lesions. Fomite transmission can also occur.

Pathogenesis

- Diphtheria is initiated by entry of *C. diphtheriae* into the nose or pharynx. It multiplies locally without blood stream invasion.
- It produces a powerful exotoxin which causes local tissue necrosis, and formation of a tough, adherent pseudomembrane, composed of a mixture of fibrin, dead cells, and bacteria. The membrane usually begins on the tonsils or posterior pharynx and can spread to fauces, soft palate, and into the larynx, which may result in respiratory obstruction. Toxin entering the blood stream causes tissue damage at distant sites, particularly the heart (myocarditis), nerves (demyelination), and kidney (tubular necrosis).
- Nontoxigenic strains may cause mild local respiratory disease, sometimes including a membrane.

Clinical Features

Respiratory Diphtheria

- Nose infection presents as a chronic serosanguineous or seropurulent discharge without fever or significant toxicity. A whitish membrane may be observed on the septum.

- The faucial (pharyngeal) form is most common. After an incubation period of 1 to 7 days, the illness begins with a sore throat, malaise, and mild to moderate fever. Grayish membrane may be present that is tightly adherent and bleeds on attempted removal. In severe cases, the patient appears toxic. Cervical lymphadenopathy and soft tissue edema may occur, resulting in the typical *bull neck appearance* and stridor.
- Laryngeal involvement presents as hoarseness, stridor, and dyspnea.
- Myocarditis presents with signs of low cardiac output and congestive failure. Conduction disturbances, ST-T wave abnormalities, arrhythmias, and heart block can occur.
- Neurologic involvement manifests as cranial nerve palsies and peripheral neuritis. Palatal and/or pharyngeal paralysis occurs during the acute phase.

Cutaneous Diphtheria

- Cutaneous diphtheria lesions are classically indolent, deep, punched-out ulcers, which may have a grayish white membrane.

Invasive Disease

- This is rare and may cause endocarditis, osteomyelitis, septic arthritis, and meningitis. Frequently, these patients have underlying immunosuppression.

Investigations

- *Gram's stain*: A presumptive diagnosis of *C. diphtheriae* can be made by identifying gram-positive rods in a "Chinese letter" distribution on Gram's stain.
- Cultures from beneath the membrane, from the nasopharynx, and from suspicious skin lesions. Cultures may be negative if the patient has received antibiotics.
- Toxigenicity testing should be performed on all *C. diphtheriae* isolates.
- Polymerase chain reaction test may allow both detection of the organism and determination of toxigenicity.
- ECG may show ST-T wave changes, heart block, and dysrhythmia.

Treatment

- The goals of treatment are to neutralize the toxin, eliminate the infecting organism, provide supportive care, and prevent further transmission.

Antitoxin

- Diphtheria antitoxin is a hyperimmune antiserum produced in horses, which binds to and inactivates the diphtheria toxin.
- The antitoxin is only effective before toxin enters the cell and thus must be administered as early as possible.
- There is risk of allergic reactions to antitoxin since it contains horse serum. Hence, a test dose should be given before administration.
- The dose of antitoxin depends upon the site and severity of infection. 20,000 to 40,000 units for pharyngeal/laryngeal disease, 40,000 to 60,000 units for nasopharyngeal disease, and 80,000 to 120,000 units for severe disease with "bull-neck". The dose should be administered intravenously over 60 minutes.

Antibiotics

- They decrease toxin production indirectly by killing the organisms.
- Penicillin is the drug of choice. Penicillin G (25,000 to 50,000 units/kg IV Q12 h until the patient can take orally) followed by oral penicillin V (250 mg QID) for a total of 14 days.
- Erythromycin 500 mg QID for 14 days is an alternative.

Diphtheria Toxoid

- Patients should be given diphtheria toxoid immunization during their convalescence since natural infection does not induce immunity.

Prevention

- Isolate the patient.
- Non-immunised contacts should be given both antibiotics and diphtheria antitoxin.
- Immunised contacts are given a booster dose of diphtheria toxoid.

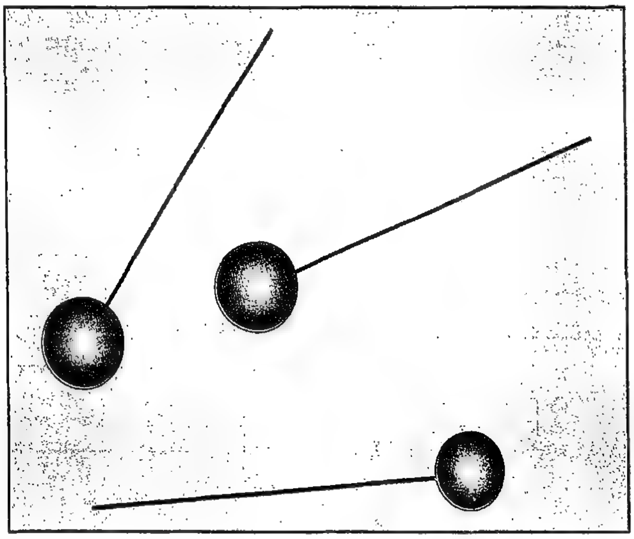

Fig. 1.3: Tetanus bacilli

Q. Describe the etiology, pathogenesis, clinical features and management of tetanus. Add a note on prevention of tetanus.

- Tetanus is a serious illness caused by *Clostridium tetanus* organism. It is characterized by an acute onset of hypertonia, painful muscular contractions (usually of the muscles of the jaw and neck), and generalized muscle spasms.
- Tetanus has been described by Hippocrates and in the Indian medical writings of Sushruta.

Etiology

- *Cl. tetanus* is a Gram-positive, spore-forming, anaerobic bacillus. It has a drumstick appearance due to the presence of terminal spore. It is a normal commensal of human and animal gastrointestinal tracts and is widely distributed in soil. Its spores can survive for many years even in adverse conditions.
- Tetanus can occur in the following situations:
  - *Neonatal tetanus*: Occurs when the umbilical cord is cut with an unsterile instrument or smeared with cowdung after cutting as is the practice in some areas.
  - After road traffic accidents where wounds may get contaminated easily with tetanus spores. Even a seemingly trivial injury may be able to cause tetanus.
  - People with otorrhoea may develop tetanus if the ear is probed with a wire or matchstick which may carry spores on it.
  - In women after illegal abortion due to unsterile handling of the genital tract through which organisms gain entry.
  - Intramuscular injections given with contaminated needles.
  - Necrotic or gangrenous tissues due to peripheral vascular disease or any other cause.

Pathogenesis

- Spores inoculated into the wound develop into bacteria. These bacteria multiply locally and produce neurotoxin tetanospasmin which is responsible for the clinical manifestations of tetanus.
- Toxin released in the wound is disseminated throughout the body and binds to motor neuron terminals in muscles, and ascends up the axon to reach nerve-cell body in the brainstem and spinal cord. The toxin then migrates across the synapse to presynaptic terminals where it blocks release of the inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA). As a result, minor stimuli result in uncontrolled spasms, and reflexes are exaggerated.
- The time taken for the toxin to ascend from nerve endings to CNS depends on the length of nerves. Since cranial nerves are short, effect is first seen in cranial nerve territories like lock jaw.

Clinical Features

- The incubation period is 5 days to 15 weeks.
- Tetanus can present in one of four clinical patterns:
  - Generalized
  - Local
  - Cephalic
  - Neonatal

Generalized Tetanus

- This is the most common and most severe form.
- The classical clinical triad consists of trismus (lock jaw), muscle rigidity, and reflex spasms.
- Tetanic spasms mainly affect the muscles of the trunk, back and proximal parts of the limbs, and spare the peripheries.
- The patient first notices difficulty in opening the jaw due to increased tone in the masseter muscles (trismus, or lock jaw). Dysphagia or stiffness or pain in the neck, shoulder, and back muscles appears concurrently or soon thereafter. Abdominal and limb muscle involvement produces a rigid abdomen and stiff limbs. Sustained contraction of the facial muscles results in a grimace or sneer (risus sardonicus), and contraction of the back muscles produces an arched back (opisthotonus).
- Chest muscle spasms impair breathing. Laryngospasm may produce asphyxia.
- These spasms occur repetitively and may be spontaneous or provoked by even the slightest stimulation. They occur several hundred times a day.
- Tetanic spasms cause contraction of both agonist and antagonist groups of muscles together.
- Patient remains fully conscious and alert throughout, even during spasms.
- Autonomic dysfunction is seen in severe cases and is characterized by labile or sustained hypertension, tachycardia, dysrhythmia, hyperpyrexia, profuse sweating, peripheral vasoconstriction, and increased plasma and urinary catecholamine levels.
- Patient may develop many complications like aspiration pneumonia, fractures, muscle rupture, rhabdomyolysis, deep vein thrombophlebitis, pulmonary embolism.

Local Tetanus

- Uncommon form in which manifestations are restricted to muscles near the wound. The prognosis is excellent.

Cephalic Tetanus

- Rare form of local tetanus, follows head injury or ear infection. Trismus and dysfunction of one or more cranial nerves, often the seventh nerve, are found. Cephalic tetanus may remain localized or may progress to generalized tetanus. The incubation period is a few days and the mortality is high.

Neonatal Tetanus

- Neonatal tetanus (tetanus neonatorum) is generalized tetanus that results from infection of a neonate.

Differential Diagnosis

- Inflammatory lesions inside the mouth can induce trismus (lock jaw).
- Drug induced dystonic reactions (e.g. phenothiazines, metoclopramide).
- Strychnine poisoning.
- Hypocalcemic tetany.

Treatment

- The goals of therapy are to eliminate the source of toxin, neutralize unbound toxin, prevent muscle spasms, and support the patient until recovery. Patient should be kept in a quiet room to minimize stimulation. Patient should be continuously monitored for any sign of deterioration especially respiratory compromise.

Antibiotic Therapy

- Antibiotics are given to kill tetanus bacilli so that further production of toxin is prevented.
- Penicillin is the drug of choice (10 to 12 million units intravenously, in divided doses daily for 10 days). Metronidazole is an alternative. Clindamycin and erythromycin can be used in those allergic to penicillin.

Antitoxin

- Antitoxin is given to neutralize the free circulating and unbound toxin. It does not have any action on the bound toxin.
- Human anti-tetanus globulin (ATG) is the choice and is given in a dose of 3000 to 6000 units intramuscularly, usually in divided doses because the volume is large. Human antitetanus immunoglobulin has a long half life; hence repeated doses are not required.
- Equine anti-tetanus immunoglobulin can also be used but carries risk of allergic reactions. However, it is cheaper.
- The value of injecting antitoxin proximal to the wound or infiltrating around the wound is unclear. Antitoxin does not penetrate the blood–brain barrier. The value of intrathecal administration is still not clear.

Control of Muscle Spasms

- Benzodiazepines like diazepam, lorazepam and midazolam can be used to control muscle spasms.
- Uncontrolled spasms even after giving benzodiazepines may reuire paralysis with a nondepolarizing neuromuscular blocking agent and mechanical ventilation.
- General anesthesia with propofol may be required for continuous spasms.
- Dantrolene and intrathecal baclofen can also be considered in severe spasms.

Supportive Measures

- Respiratory support with endotracheal intubation or tracheostomy, and mechanical ventilation, may be required.
- IV fluids should be given to maintain hydration.
- Hypertension due to autonomic dysfunction may be controlled by beta blockers, clonidine, and morphine sulfate.
- Hypotension or bradycardia may require volume expansion, use of vasopressors.
- Wound should be kept clean by debridement and removing any necrotic or foriegn material.

Prevention of Tetanus

Immunization

- All partially immunized and unimmunized adults should receive vaccine, as should those recovering from tetanus. The primary series for adults consists of three doses: the first and second doses are given 4 to 8 weeks apart, and the third dose is given 6 to 12 months after the second. A booster dose is required therafter every 10 years.
- For persons with unclean and major wounds, give tetanus immunoglobulin 250 units IM and also a dose of tetanus vaccine.

Wound Care

- Wounds should be washed thoroughly and any dead tissue and slough should be excised

Q. Discuss the etiology, pathogenesis, clinical features, diagnosis and treatment of botulism.

- Botulism is a paralytic disease caused by botulinum toxin, which is produced by *Clostridium botulinum*.
- *C. botulinum* is an anaerobic gram-positive organism that forms subterminal spores. It is is found in soil and marine environments throughout the world. Botulinum toxin is the most potent bacterial toxin known.

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Pathogenesis

- Under anaerobic conditions, the spores germinate and the bacteria multiply and release the exotoxin. Botulinum toxin inhibits release of acetylcholine at the neuromuscular junction and causes flaccid paralysis. Botulinum toxin is extremely potent and is capable of killing a person even in minute quantities. It can be used as an agent of bioterrorism.
- Naturally occurring botulism occurs in one of three forms: Food-borne botulism, infant botulism, or wound botulism. Food-borne botulism is caused by ingestion of preformed toxin present in canned foods. Infant botulism occurs due to the practice of feeding honey to infants. Honey may contain botulism organisms and proligerate in the gut to produce toxin. Wound botulism usually occurs due to contamination of wound with organisms.

Investigations

- Toxin can be identified in serum, stool, vomitus, gastric aspirate, and suspected foods.
- *C. botulinum* may be grown on selective media from samples of stool or foods.
- Wound cultures that grow *C. botulinum* suggest wound botulism.

Clinical Features

- Symmetric descending paralysis is characteristic and usually starts in the extraocular muscles, and spreads to the pharynx, larynx, and respiratory muscles before inducing a generalised flaccid paralysis. Patient may have symptoms like ptosis, blurred vision, diplopia, pooling of secretions, dysphagia and breathlessness.
- Nausea, vomiting and diarrhea may occur if the source of toxin is intestine. Paralytic ileus may develop due to intestinal muscles paralysis.
- Fever is unusual.
- Patient is conscious and alert.
- Sensory findings are usually absent.
- Respiratory paralysis may lead to death in untreated cases.
- A diagnosis of botulism must be considered in patients with symmetric descending paralysis who are afebrile and mentally intact.

Treatment

- Botulinum antitoxin should be given intravenously as early as possible.
- Antibiotics are recommended for wound botulism along with incision and thorough debridement of the infected wound. Penicillin G or metronidazole can be used.
- The immediate threat to life is respiratory failure. Close monitoring for respiratory failure is important. If respiratory failure develops, endotracheal intubation and mechanical ventilation should be started. Tracheostomy is required if the patient needs mechanical ventilation for a long time.

Q. Gas gangrene.

- *Gas gangrene* (also known as *clostridial myonecrosis*) is a bacterial infection that produces gas in tissues in gangrene. It usually occurs as a complication in devitalised and devascularised tissues. It is a medical emergency.

Etiology

- 80% of cases are caused by *Clostridium perfringens*, while *C. novyi, C. septicum*, and *C. histolyticum* cause the remaining cases. These organisms are true saprophytes and are ubiquitous in soil and dust.
- *C. perfringens* grows in anaerobic conditions and also produces a toxin, and enzymes like collagenases and hyaluronidases which destroy the connective tissue and allow the infection to spread.

Clinical Features

- The incubation period of gas gangrene is usually short; less than 3 days.
- The first symptom is pain, along with numbness of the affected limb. There may be swelling around the wound, with pale surrounding skin. Serosanguinous foul-smelling discharge may be there from the wound. Crepitus can be elicited on palpation in and around the wound due to gas formation.
- Constitutional symptoms are severe with tachycardia and hypotension and the patient may be stuporose. Mild to moderate fever may be there.
- Sometimes uterine infection can occur following criminal abortion or poor aseptic technique during labor.

Laboratory Findings

- Gas gangrene is a clinical diagnosis, and empiric therapy should be started if the diagnosis is suspected.
- X-rays may show presence of gas in the tissues.
- The smear shows the presence of gram-positive rods.
- Anaerobic culture confirms the diagnosis.

Treatment

- Wounds should be thoroughly cleansed and debrided.
- Traditionally, the antibiotic of choice for clostridial infection has been penicillin G (4 million units every

four hours IV). Recently clindamycin has shown to be superior to penicillin G. Combination of clindamycin and penicillin is superior to penicillin alone. Metronidazole can be used instead of clindamycin.
- Antitoxin is of doubtful value.
- Hyperbaric oxygen may relieve constitutional symptoms but its effect on mortality is not clear.

Q. Describe the etiology, pathogenesis, clinical features and treatment of pseudomembranous colitis.

Etiology

- Pseudomembranous colitis is inflammation of the colon that occurs in some people who have taken antibiotics. It is usually caused by *Clostridium difficile* and occurs a few days after starting antibiotic therapy.
- Broad spectrum antibiotics such as clindamycin and ampicillin have been implicated most often, but tetracyclines and cephalosporins are other causal agents.

Pathogenesis

- *C. difficile* colonizes the intestinal tract after the normal gut flora has been altered by antibiotic therapy.
- After colonization, *C. difficile* elaborates two large toxins: Toxin A an enterotoxin, and toxin B a cytotoxin. These toxins initiate an inflammatory process in the intestinal mucosa resulting in the disruption of epithelial-cell barrier function, diarrhea, and pseudomembrane formation.

Clinical Features

- Bloody diarrhea.
- Fever and abdominal pain.
- Signs of dehydration may be there due to diarrhea.
- Toxic megacolon and colonic perforation (rigid abdomen and rebound tenderness) can occur in most severe cases.

Investigations

- Stool examination may show presence of WBCs.
- Culture for *C. difficile* is slow and expensive, hence not recommended.
- Stool assay for *C. difficile* toxins (mostly toxin B). It is considered positive when cultured cells undergo cytopathic changes when exposed to stool which contains toxin.
- Enzyme-linked immunoabsorbent assay (ELISA) for toxin A.
- Sigmoidoscopy may reveal erythematous mucosa covered by adherent membranes over the colonic mucosa.

Treatment

- All antibiotics should be stopped and this alone may halt the diarrhoea.
- If patient is very sick, vancomycin (125 mg orally 4 times daily for 14 days) or metronidazole (500 mg orally 3 times daily for 14 days) may be used to treat diarrhea.
- Fidaxomicin is a macrolide antibiotic that is more effective than vancomycin in cancer patients.
- Probiotics such as lactobacillus may be considered but benefit is doubtful.
- Surgery may be required for complications such as toxic megacolon, perforation and necrotizing colitis.

Q. Anthrax (malignant pustule, woolsorters, disease, Siberian ulcer, charbon).

- Anthrax is a zoonotic infection caused by *Bacillus anthracis*. Anthrax is also known by various names like malignant pustule, woolsorters' disease, Siberian ulcer, charbon, etc.

Etiology

- *B. anthracis* is a sporulating gram-positive rod.
- Actually it is a zoonotic infection which affects sheep, cattle, horses and goats. Humans are affected when spores are ingested or inhaled or inoculated into broken skin. This can happen either by direct contact with these animals or contact with their products.
- Recently anthrax has attained notoriety because of its possible use in biological warfare.

Pathology

- After entry into the body, the spores germinate into vegetative bacteria and multiply locally.
- Spores entering the lungs are ingested by macrophages and carried via lymphatics to regional lymph nodes, where they rapidly multiply and cause hemorrhagic lymphadenitis.
- Invasion of the bloodstream leads to sepsis, killing the host.

Clinical Features

- The incubation period is from 1 to 5 days.
- Depending on the route of entry, anthrax occurs in three forms: cutaneous, inhalational, and gastrointestinal forms.
- Cutaneous anthrax is the most common presentation (95%). Spores inoculate a host through skin lacerations, abrasions, or biting flies. This form most commonly affects the exposed areas of the upper extremities. Initially the cutaneous lesion appears as a small erythematous, maculopapular lesion, which subsequently

undergoes vesiculation and ulceration to form a black eschar (malignant pustule). Sometimes sloughing of the eschar is associated with hematogenous spread, sepsis and shock.

- Respiratory involvement (woolsorters' disease) is due to inhalation of spores, resulting in nonproductive cough, fever and retrosternal discomfort. Occasionally initial clinical improvement is followed by severe dyspnoea, stridor, cyanosis and death. Neck and chest wall edema may develop.
- Gastrointestinal infection occurs after ingestion of spores and presents as diarrhea and vomiting, which can be bloody.

Investigations

- *Chest X-ray* may show mediastinal widening in inhalational anthrax.
- *Gram stain*—gram-positive rods seen.
- *Culture* may grow *B. anthracis*.
- *Serological studies* may demonstrate antibodies to Anthrax bacillus.

Treatment

- ***First-line agents***: Ciprofloxacin, doxycycline.
- ***Second-line agents***: Amoxicillin, penicillin G.
- Combination therapy is more likely to result in a cure than monotherapy. Systemic anthrax should always be treated with combination of three drugs.

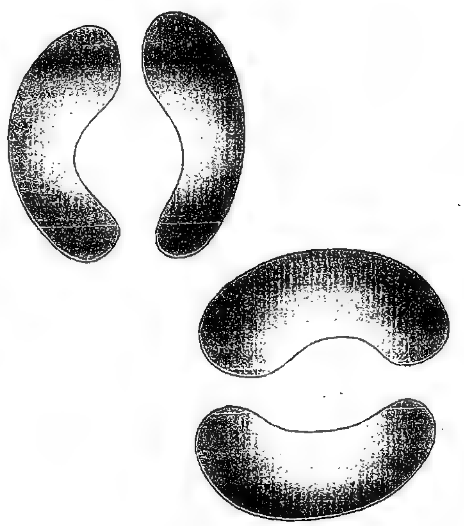

Fig. 1.4: Gonococci

Q. Gonorrhea; Gonococcal urethritis.

- Gonorrhea is a sexually transmitted disease (STD) characterized by purulent infection of the mucous membrane surfaces.
- It is one of the commonest STDs world over.

Etiology

- It is caused by a gram-negative diplococcus *Neisseria gonorrhea* which infects the epithelium of the urogenital tract, and less frequently of the rectum and the conjunctivae. Gonococci are kidney shaped, and occur in pairs, hence the name gonococcus.

Clinical Features

- The incubation period is 1–5 days. The common age group affected is 15–30 years.
- Females act as carriers and suffer from more complications than males.
- Asymptomatic infections also occur and more common in females. Asymptomatic individuals contribute more to transmission of infection than actual cases.
- Gonococcal infection in males results in acute urethritis with symptoms of dysuria and purulent urethral discharge. Some patients may have mucoid urethral discharge. It may spread and cause epididymitis and prostatitis.
- In females, cervix is infected more often than the urethra. Vaginal discharge, discomfort and dysuria are common symptoms.
- Rectal gonorrhea (proctitis) occurs in homosexual males and heterosexual females as a result of ano-genital sex. The symptoms vary from mild anal pruritus and mucopurulent discharge to symptoms of severe proctitis with rectal pain and tenesmus.
- Pharyngeal gonorrhea (pharyngitis) may occur as a consequence of oro-genital sex and may be seen in either sex. This is generally asymptomatic.
- Ocular gonorrhea is rare in adults. It occurs in neonates as a result of contact of eyes with the infected maternal birth canal. It presents as acute purulent conjunctivitis that may affect deeper structures of the eye and may occasionally result in panophthalmitis.

Complications

- In males—epididymitis
- In females—endometritis, salpingitis, tubo-ovarian abscess, bartholinitis, peritonitis, and pelvic inflammatory disease.
- Disseminated gonococcal infection may lead to skin lesions, tenosynovitis, arthritis, and (in rare cases) endocarditis or meningitis.

Investigations

- ***Gram stain***: Presence of typical gram-negative intracellular diplococci establishes a diagnosis of gonorrhea.
- Culture
- Polymerase chain reaction (PCR).

Treatment

- Ceftriaxone 250 mg intramuscular (IM) single dose PLUS, azithromycin 1 g PO single dose OR doxycycline 100 mg PO twice a day for 7 days
- Quinolones like ciprofloxacin (500 mg) or levofloxacin (250 mg) are alternatives but resistance is emerging.
- Spectinomycin, 1 g intramuscularly once, may be used for the penicillin-allergic patient.

Q. Chancroid.

- Chancroid also known as "soft chancre", is a sexually transmitted disease (STD) characterized by painful genital ulcers that may be accompanied by inguinal lymphadenopathy.

Etiopathogenesis

- Chancroid is caused by *Haemophilus ducreyi* which is a small gram-negative bacillus. When examined by gram stain, organisms from culture often clump in long parallel strands, producing a so-called "school of fish" appearance. It is highly infectious.
- It is pathogenic only in humans, with no intermediary host. *H. ducreyi* is transmitted sexually by direct contact with purulent lesions and by autoinoculation to nonsexual sites, such as the eye and skin. *H. ducreyi* enters the skin through disrupted mucosa and causes a local inflammatory reaction. It produces a cytotoxin which plays a role in epithelial injury and development of an ulcer.

Epidemiology

- It is seen worldwide, and is associated with low socio-economic and poor hygienic conditions. Chancroid is most often seen in uncircumcised men. In women it may be asymptomatic.

Clinical Features

- Incubation period is 4–7 days.
- The ulcer is seen on the prepuce in men and on the labia in women. It begins as a papule with surrounding erythema which ruptures and forms an ulcer. Ulcers are usually multiple, painful, non-indurated and soft, has undermined edges with a base of granulation tissue and slough.
- Tender inguinal lymphadenopathy occurs in about half the patients. These lymph nodes may become fluctuant (bubo) and rupture spontaneously.

Diagnosis

- Gram stain of material from a bubo reveals large numbers of gram-negative coccobacilli, arranged in a 'school of fish' pattern.
- Culture is the most definitive method of diagnosis, but the organism is fastidious.
- Immunofluorescence test and serologic assays for antibodies are newer laboratory tests.

Differential Diagnosis

- Chancroid ulcer has to be differentiated from genital ulcer due to syphilis, lymphogranuloma venereum, herpes simplex virus-2, and granuloma inguinale.

Treatment

- A single 1 g oral dose of azithromycin will cure most people.
- Alternative regimens include ceftriaxone (250 mg intramuscularly as a single dose), or ciprofloxacin (500 mg orally twice a day for 3 days), or erythromycin (500 mg orally three times a day for 7 days).
- Fluctuant lymph nodes may require needle aspiration or incision and drainage.

Q. Pertussis (whooping cough).

- Pertussis (*per*: intensive, *tussis*: cough) is an acute respiratory tract infection caused by *Bordetella pertussis,* a gram-negative coccobacillus.
- A severe bout of cough is followed by a deep inspiration with characteristic sound (whoop). Hence the name "whooping cough."
- The Chinese name for pertussis is "the 100-day cough," which accurately describes the course of the disease.

Epidemiology

- Pertussis occurs worldwide but the incidence has come down due to vaccination. Periodic epidemics, however, continue world over.
- The infection is more common and serious in infancy and early childhood. It is highly communicable.
- Even with the decline after vaccination, pertussis still continues to be a major health hazard.

Pathogenesis

- The organism is spread by droplets from patients.
- Infection is initiated by attachment of the organism to the ciliated epithelial cells of the nasopharynx. Attachment is mediated by surface adhesions. At the site of attachment, the organism multiplies, producing a variety of toxins that cause local mucosal damage and systemic effects. There is local cellular invasion, but systemic dissemination does not occur. Systemic manifestations are due to toxins.

- It is not exactly known what causes the paroxysmal cough that is the hallmark of pertussis. Pertussis toxin may be responsible for cough. Local mucosal damage may contribute.
- Bronchopneumonia can develop in some persons.
- Seizures and encephalopathy can occur and are due to hypoxia from coughing paroxysms or apnea.

Clinical Features

- The incubation period is 7 to14 days.
- Classically, there are three stages: Catarrhal, paroxysmal and convalescent.

The Catarrhal Stage

- Lasts 1–2 weeks. It resembles common cold and is characterised by running nose, fever and mild cough.

Paroxysmal Stage

- Lasts for 2–6 weeks or longer. The cough becomes more frequent and spasmodic with repetitive bursts of 5 to 10 coughs, often within a single expiration. The episode may be terminated by an audible whoop, which occurs due to rapid inspiration against a closed glottis at the end of a paroxysm. Post-tussive vomiting is frequent.
- During a spasm, there may be impressive neck-vein distension, bulging eyes, tongue protrusion, and cyanosis.
- Paroxysms may be precipitated by noise, eating, or physical contact.
- The whoop may be absent in infants, partially immune older children, and adults, which makes the diagnosis difficult in them. Most complications occur during the paroxysmal stage.

The Convalescent Stage

- Decrease in intensity and frequency of the cough over 1–2 weeks.

Differential Diagnosis

- Includes conditions with severe cough lasting more than 2 weeks. These are adenovirus infection, endobronchial tuberculosis, inhaled foreign body, and hyperreactive airway disease.

Complications

- Infants and young children have more complications.
- Respiratory complications: Otitis media, pneumonia due to *B. pertussis* itself or secondary bacterial infection, atelectasis, emphysema, bronchiectasis, pneumothorax and pneumomediastinum.
- *Neurological complications*: Seizures and encephalopathy.
- Severe cough leads to marked increase in pressure in various body compartments, which may cause epistaxis; retinal, subconjunctival and intracranial hemorrhage; inguinal hernia; rectal prolapse; rupture of the diaphragm; rib fracture.
- Malnutrition can occur due to prolonged disease.

Laboratory Findings

- Pertussis is mainly a clinical diagnosis.
- There may be lymphocytic leucocytosis.
- Confirmation of diagnosis depends on culture of *B. pertussis* from a nasopharyngeal swab or cough plate in Bordet-Gengou medium. Cultures are often positive in the catarrhal and early paroxysmal stage.
- Direct fluorescent antibody and counter-immuno electrophoresis are other methods for rapid diagnosis.

Management

- Patient should be admitted to hospital if there is respiratory distress, neurological signs and dehydration.
- *Antibiotics:* Purpose is to eradicate the infecting bacteria from the nasopharynx. Antibiotics should be given early to reduce the risk of prolonged disease. Macrolide antibiotics (azithromycin, clarithromycin) are the drugs of choice for treatment of pertussis. Trimethoprim-sulfamethoxazole is an alternative for individuals allergic to macrolides.
- *Supportive measures:* These provide adequate nutrition and hydration and avoiding factors aggravating cough such as excessive crying. Complications are managed as per standard guidelines.

Prevention

- Isolate the patient for 4–5 days after starting antibiotics to prevent spread to others.
- Chemoprophylaxis with erythromycin is recommended for close family contacts especially under 2 years of age. Children under 5 years of age should be vaccinated.

Q. Discuss the etiology, pathogenesis, clinical features, diagnosis and management of typhoid fever (enteric fever).

Q. Rose spots.

Q. Complications of typhoid fever.

- Typhoid is a systemic infection caused by *Salmonella typhi* or *paratyphi*.
- The disease was initially called typhoid fever because of its clinical similarity to typhus. Since the primary site

of infection is intestine, the term enteric fever was proposed as an alternative name. However, to this day, both names are used interchangeably.

Etiology

- Salmonella are gram-negative, motile, non-lactose fermenting bacilli. Salmonellae are present worldwide but cause disease only where poor hygiene and overcrowding exist.

Pathogenesis

- Humans are the only reservoir of *S. typhi*. Organisms originate from patients with typhoid, or from carriers excreting organisms in their stools. Human hands, flies, or insects then transfer these organisms to food or drink. Since *S. typhi* survive freezing and drying, infection can also occur through ice or canned food. Shellfish from polluted waters may transmit the disease. Decreased stomach acidity is a risk factor for infection to occur.
- Once salmonellae reach the small intestines, the bacteria penetrate and traverse through the intestinal wall through phagocytic cells that reside within Peyer's patches. After crossing the epithelial layer of the small intestine, *S. typhi* and *S. paratyphi* are phagocytosed by macrophages.
- Once phagocytosed, salmonellae disseminate throughout the body in macrophages via the lymphatics and colonize reticuloendothelial tissues (liver, spleen, lymph nodes, and bone marrow) where they start multiplying. Patients have relatively a few or no signs and symptoms during this initial incubation stage.
- Once the number of bacteria reaches a critical stage, they invade blood stream and rest of the body. At this stage, signs and symptoms, such as fever and abdominal pain appear. Peyer's patches can get enlarged and necrosed due to mononuclear cell infiltration. Bacteria also reach galbladder via blood stream and multiply there. From the gallbladder, bacteria reach the intestine and are excreted in the stool which can spread to others via contaminated foods. Some patients become chronic carriers carrying the bacteria in their gallbladder and are responsible for much of the transmission of the organism. While asymptomatic, they may continue to shed bacteria in their stool for decades.

Clinical Features

- The incubation period averages 10 to 14 days.
- The onset of the disease is insiduous, with headache, malaise, anorexia and fever. The fever is remittent (does not touch the baseline) sometimes increasing in a step-like manner (step ladder fever) to reach a peak towards the end of the first week. Thereafter, it plateaus and remains for two to three weeks. Accompanying chills are common but frank rigors are rare. Headache is present and often disabling.
- With the passing days debility sets in and in some cases progresses to mental dullness and delirium, characterized by muttering and picking at the bedclothes.
- Abdominal discomfort with mild bloating and constipation usually occurs, but diarrhea can also occur. Stools may have a 'pea soup' appearance.
- Hepatosplenomegaly may develop by the end of the first week. Mild jaundice may be present.
- The typical rash of typhoid (rose spots) develops in the second week but is seldom seen in Indian patients. "Rose spots" are macules, 2–3 mm in size, occur in small crops on the chest and abdomen, blanch on pressure and last for 2–3 days.
- In the absence of complications, typhoid fever usually subsides.

Complications

- Complications are uncommon now due to availability of effective antibiotics.
- *Bleeding*: Erosion of blood vessels in necrotic Peyer's patches or in the intestinal wall can initiate bleeding.
- *Intestinal perforation*: Typhoid ulcers can perforate. Usually happens in 3rd week of illness.
- Typhoid can affect almost all the organs. Hence, pneumonia, meningitis, nephritis, cholecystitis, hepatitis, myocarditis, osteomyelitis, encephalitis can occur.
- Involvement of the central nervous system can present as stupor, delirium, convulsions, encephalitis, cerebellar ataxia, extrapyramidal signs, myopathy and deafness.
- Acute renal failure and disseminated intravascular coagulation are rare complications.

Investigations

- The diagnostic "gold standard" for enteric fever is culture of *S. typhi* or *S. paratyphi*. Blood cultures are positive in 90% during the first week of infection but decrease to 50% by the third week. Cultures of stool and urine may also be positive. Bone marrow culture is highly (90%) sensitive and may remain positive even with up to 5 days of antibiotic therapy. Culture of intestinal secretions (best obtained by a noninvasive duodenal string test) can be positive despite a negative bone marrow culture. If blood, bone marrow, and intestinal secretions are all cultured, the yield of a positive culture is >90%. Stool cultures, can be positive during the third week of infection in untreated patients.

- The Widal test is very helpful in diagnosis. There can be false positive and false negative results. The test is positive if O antigen titer is more than 1:160. A four-fold rise in serum agglutinins against the somatic (O) antigen of the bacillus is diagnostic rather than a single test. Titres against the flagellar (H) antigen are less specific. Usually it becomes positive after the 1st week of illness. Early antimicrobial therapy may dampen the immunologic response.
- Relative bradycardia and leukopenia may be a clue to diagnosis.
- LFT may show mild elevation of AST and ALT.
- Polymerase chain reaction tests and DNA probe assays are being developed.

Treatment

- Third generation cephalosporins are currently the drugs of choice. Ofloxacin and levofloxacin are also effective, but quinolone resistance is now emerging.
- Ceftriaxone (1 to 2 g intravenously or intramuscularly) for 10 to 14 days is the treatment of choice in severe typhoid.
- Azithromycin is also an alternative to quinolones (1 g orally once a day for 7 days or 1 g orally on day 1 followed by 500 mg orally for 10 days).
- Paracetamol can be used to control fever, headache and myalgia.
- Other supportive measures include good nutrition and hydration. Soft and bland diet should be given because of inflamed bowel. Laxatives and enemas should be avoided because of the same reason.
- In cases of severe typhoid fever (fever, altered sensorium or septic shock; and a positive culture for *S. typhi* or *S. paratyphi A*), dexamethasone treatment should be considered. One trial showed that treatment with dexamethasone decreased the mortality rate.
- About 1 to 4% patients become chronic carriers of typhoid bacilli. They can be a source of infection to others (remember Typhoid Mary). Carrier state can be treated with oral amoxicillin, TMP-SMX, ciprofloxacin, or norfloxacin. Antibiotics should be given for 6 weeks. However, in cases of anatomical abnormality (e.g. biliary or kidney stones), eradication of the infection often cannot be achieved by antibiotic therapy alone and requires surgical correction of the abnormalities.

Prognosis

- The mortality rate of typhoid fever is about 2% in treated cases. Elderly or debilitated persons are likely to do poorly. With complications, the prognosis is poor. Relapses occur in up to 15% of cases.

Q. Typhoid vaccines.

- Vaccination against typhoid is recommended for:
  - Persons traveling to developing countries
  - People who have intimate or household contact with a case or chronic carrier
  - Laboratory workers who frequently work with *S. typhi*.
- Following typhoid vaccines are currently available. None of the typhoid vaccines protect against paratyphoid fever.

1. Ty21a (oral vaccine)

- This is an attenuated live *S. typhi* vaccine. The vaccine is supplied as a packet of four enteric-coated capsules that must be kept refrigerated. It should be given as one capsule every other day until all four capsules have been taken. Booster doses are given every 5 years. Vaccine-elicited immunity occurs 14 days after receipt of the last dose, with an efficacy of 50 to 80 percent. It maintains its efficacy for 4 years. It is well tolerated. Ty21a is commonly used vaccine because it can be given orally and has fewer side effects.
- It is contraindicated in:
  - Pregnant women
  - Children below 6 years.
  - People with immunodeficiency.

2. ViCPS

- It consists of purified Vi polysaccharide from the bacterial capsule.
- It is given as 0.5 ml intramuscularly (single dose) and is well tolerated. It maintains its efficacy for 2 years. Booster dose is given after 2 years.
- It should not be used below 2 years.

3. Vi-rEPA

- This vaccine consists of Vi polysaccharide bound to a non-toxic recombinant protein that is identical to *Pseudomonas aeruginosa* exotoxin A.
- Coupling of the Vi polysaccharide to exotoxin A results in impressive T cell responses. In a trial in 2 to 5 year-old children, the vaccine provided 90% efficacy and was very well tolerated, with no serious adverse reactions. Trials of this vaccine in adults and infants are underway.
- Two parenteral doses are given.

Q. Typhoid carrier.

- A person who excretes salmonella organism in stool for more than 12 months after the acute infection is called chronic carrier.
- About 1 to 6 percent patients become chronic carriers after *Salmonella typhi* infection, and the rate is higher in patients with cholelithiasis or other biliary tract abnormalities.

- Chronic urinary carriage of *S. typhi* is rare and is usually associated with urinary tract abnormalities such as urolithiasis, prostatic hypertrophy or *Schistosoma haematobium* infection.
- Chronic carriers do not develop recurrent symptomatic disease. They develop high level systemic immunity so that they do not develop clinical disease but excrete large numbers of organisms in the stool.
- Chronic carriers act as source of infection to others, particularly if involved in food preparation. Hence, eradication of carrier state should be done if such individuals are identified.

Treatment

- Fluoroquinolones are the drugs of choice to eradicate carrier state (e.g. ciprofloxacin 500 to 750 mg orally twice daily or ofloxacin 400 mg orally twice daily for 4 weeks). Cholecystectomy should be considered if there is any abnormality such as cholelithiasis.
- Alternatives are ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol.

Q. Shigellosis.

Etiology

- Shigellosis refers to infection of the intestinal tract by shigella species.
- There are 4 species; *Shigella dysenteriae, Sh. flexneri, Sh. sonnei and Sh. boydii.*
- *Shigella dysenteriae* type-1 is the most virulent of the shigellae. It has been responsible for many epidemics during war, famine and natural disasters.

Epidemiology

- Shigellosis occurs mainly in the developing countries.
- Shigella infection is associated with the 'gay bowel syndrome' of homosexuals, and travelers' diarrhea of tourists to the Third World.
- The disease spreads by faeco-oral route. Infection is transmitted on fingers and by flies, and does not require heavy contamination of food or water. Food and water contamination can cause epidemics as in refugee camps where population densities are high and hygienic standards low.
- Bacillary dysentery is also a hazard in institutions where hygiene is difficult to maintain, as in homes for the mentally handicapped, geriatric nursing homes, and day-care centers for children.

Pathogenesis and Pathology

- Shigella first multiplies in the small intestine and initially it may cause a secretory diarrhea. Thereafter, it rapidly localises to the colon, where inflammation with haemorrhage, microabscesses, ulceration, and mucus production results.

Clinical Features

- Symptoms usually start 2–3 days after exposure.
- The onset is sudden with fever, malaise, abdominal pain and watery diarrhea. This early phase reflects small intestinal involvement.
- Later when the colon gets involved there will be dysentery characterized by loose stools mixed with blood and mucus. There may be tenesmus. Severe cramping abdominal pain may be present.
- Nausea, vomiting, headache may occur.
- In children convulsions may occur due to the effect of neurotoxin.
- Sigmoidoscopy reveals hyperaemic and inflammed mucosa, with transversely distributed ulcers with ragged undermined edges, a picture which is indistinguishable at times from inflammatory bowel disease.
- Hematogenous spread may occur in malnourished infants and may cause seizures, meningitis, pulmonary infiltrates and peripheral neuropathy.
- Reactive arthritis, which is usually pauciarticular and nonsuppurative, and which spontaneously resolves within months, is another complication.
- Hemolytic-uremic syndrome (HUS) is occasionally seen in children with *S. dysenteriae* type 1 infection.

Differential Diagnosis

- Shigella dysentery has to be differentiated from other causes of dysentery such as:
  - Inflammatory bowel disease
  - *Entamoeba histolytica*
  - Salmonella
  - Enteroinvasive *E. coli*
  - Yersinia
  - *Campylobacter jejuni*
  - *Vibrio parahaemolyticus*
  - *Clostridium difficile*
- Clinically it is difficult to distinguish between these and laboratory tests may be needed. Viral gastroenteritis is not usually associated with fever and the stool does not usually contain blood or pus.

1

Table 1.5 Differential diagnosis between Shigella (bacillary) and amoebic dysentery

Bacillary dysentery	Amoebic dysentery
Ulcers are distributed transversely to long axis of gut. Ulcers are serpiginous with ragged undermined edges communicating with other ulcers	Ulcers are distributed in the long axis of gut; flaskshaped. Shape is oval with regular edges. Ulcers are deep and involve all layers of intestine.
Rarely perforate	May perforate
Mucous membrane is inflamed. Bowel wall not thickened.	Mucous membrane not inflamed. Bowel wall thickened.
Stool scanty in quantity but very frequent; bright blood red, gelatinous viscid mucus, odorless (red currant jelly appearance)	Stools are in rare quantity, mixed with blood and mucus, dark brown, foul smelling
Tenesmus common	Tenesmus uncommon
Stool microscopy: RBCs numerous and discrete. WBCs plenty. Bacteria may be visible	RBCs numerous and in clumps. WBCs scanty. *E. histolytica* trophozoites containing ingested red cells present

Laboratory Findings

- Stool shows many WBCs and RBCs.
- Stool culture is positive for shigellae in most cases.
- Serological tests are used mainly during epidemics.

Treatment

- *Fluid and electrolyte replacement*: Oral rehydration salt can be used and if the patient is unable to take orally use intravenous fluids.
- *Antibiotics*: Trimethoprim-sulfamethoxazole, one double-strength tablet twice a day for 7–10 days, or quinolones (ciprofloxacin, 750 mg twice daily, or levofloxacin, 500 mg once daily) for 3 days. Fluoroquinolones are contraindicated in pregnancy.
- Antimotility drugs such as loperamide and diphenoxylate hydrochloride with atropine may worsen the condition and are better avoided.

Q. Describe the etiology, epidemiology, clinical features, diagnosis and management of cholera. Add a note on its prevention.

- Cholera is an acute diarrheal illness caused by *Vibrio cholerae*. The hallmark of the disease is profuse secretory diarrhea. Cholera can be endemic, epidemic, or pandemic.

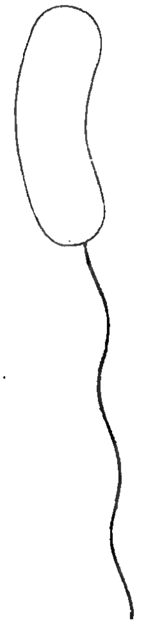

Fig. 1.5: Cholera bacillus

Etiology

- *Vibrio cholerae* is a comma shaped, motile, gram-negative bacillus that colonises the human small intestine. It has a single flagellum at one end.
- *V. cholerae* exists in two biotypes, classical and El Tor, and each biotype is further subdivided into two serotypes, Inaba and Ogawa.
- *V. cholerae* can survive in water for up to 3 weeks and on moist linen for about a week.

Epidemiology

- Its natural habitat is salt water.
- Cholera has 2 main reservoirs, humans and water. *V. cholerae* is rarely isolated from animals, and animals do not play a role in transmission of disease.
- Transmission occurs by the faeco-oral route usually through contaminated food and water.
- Pathogenic *V. cholerae* possess the 01 somatic antigen which is responsible for many epidemics and pandemics.
- Classical cholera (gravis) has been endemic from the early 1800s in the Ganges Delta of West Bengal and Bangladesh. It has been responsible for several epidemics and six pandemics in which the disease had spread from the subcontinent across the Middle East to Africa and Europe, and thence to the east coast of America.
- In 1991, epidemic El Tor struck South America.
- In 1993 an outbreak of cholera occurred in India and Bangladesh for the first time with a non 01 *V. cholerae*. This organism is now designated as 0139 Bengal. A close watch is being kept on 0139 B, as it has a potential to cause epidemics and pandemics.

Pathogenesis

- Cholera is spread by fecooral route. After ingestion, cholera bacilli colonize the small intestine, and produce an exotoxin which is responsible for the disease features.
- The exotoxin has A and B subunits. The B subunit binds to the epithelial cell wall. The A subunit is responsible for actions. A subunit activates intracellular adenylate cyclase, which causes increase in cyclic adenosine monophosphate (cAMP). cAMP in turn inhibits sodium absorption and stimulates secretion of chloride. The net effect is accumulation of sodium chloride in the intestinal lumen. Water moves passively to maintain osmolality, and when this volume exceeds the capacity of the gut to reabsorb fluid, watery diarrhea ensues.
- Cholera causes bicarbonate loss in stools and increase in lactate because of diminished perfusion of peripheral tissues which can cause metabolic acidosis. Hypokalemia results from potassium loss in the stool.
- The organisms themselves do not damage the epithelial lining cells of the gut. Since the organism does not invade the intestinal wall, stool does not contain blood.
- Malnutrition increases susceptibility to cholera. Because gastric acid can quickly inactivate *V. cholerae*, hypochlorhydria or achlorhydria of any cause (including *Helicobacter pylori* infection, gastric surgery, vagotomy, use of H_2 blockers and proton pump inhibitors) increases susceptibility. For unknown reasons, incidence of cholera appears to be twice as high in people with type O blood.

Clinical Features

- Cholera is predominantly a disease of children with attack rates highest in the 1 to 5 years age group. Classically there are three disease phases.
- *Evacuation phase*: Occurs after an incubation period of 1–2 days. There is sudden onset of painless, profuse, watery diarrhea. There may be vomiting in severe cases. Stool appears like 'Rice water' because of mucus flecks floating in the watery stools (resemblance to the water in which rice has been washed). If treament is not given at this stage, the patient passes on to the next stage.
- *Collapse phase*: This is characterised by severe dehydration with sunken eyes, hollow cheeks, 'washer-woman's hands', and decreased urine output. Circulatory shock may develop due to dehydration, with a cold, clammy skin, tachycardia, hypotension and peripheral cyanosis. The patient usually remains alert but appears weak. Muscle cramps can occur due to dehydration and hyponatermia. Children may present with convulsions due to hypoglycemia. Acute renal failure and metabolic acidosis may develop due to hypovolemic shock. If the patient survives this stage, the *recovery phase* sets in.
- *Recovery phase*: Diarrhea episodes come down and there is gradual recovery of clinical and biochemical parameters.
- *Cholera sicca*: Refers to severe disease in which massive amount of fluid and electrolytes collect in the dilated intestinal loops. Diarrhea and vomiting do not occur and the mortality is high.

Assessment of Dehydration

General condition	Well, alert	**Restless, irritable***	**Lethargic or unconscious; floppy***
Eyes	Normal	Sunken	Very sunken and dry
Tears	Present	Absent	Absent
Mouth and tongue	Moist	Dry	Very dry
Thirst	Drinks normally, not thirsty	**Thirsty, drinks eagerly***	**Drinks poorly or not able to drink***
Skin pinch	Goes back quickly	**Goes back slowly***	**Goes back very slowly***
Decision	***No dehydration***	If the patient has two or more signs, including at least one sign marked with *(star) there is ***some dehydration***	If the patient has two or more signs, including at least one sign marked with *(star) there is ***severe dehydration***

Investigations

- The diagnosis is largely clinical. It should be suspected in patients with painless diarrhea without fever and abdominal pain. Stool does not contain blood.
- Gram's stain of a stool sample may show gram negative comma shaped organisms.
- Examination of stools under dark field illumination may demonstrate rapidly motile organisms. Inhibition of their movement with type-specific antisera is diagnostic.
- Stool and rectal swabs should be taken for culture.
- Serotyping and biotyping: Specific antisera can be used in immobilization tests to identify the serotype. This is useful for epidemiologic studies.
- Hematocrit and serum protein are elevated in dehydrated patients because of hemoconcentration.

Treatment

- Cholera is simple to treat; only the rapid and adequate replacement of fluids, electrolytes, and base is required.

ORS (Oral Rehydration Salt)

- Replacement of fluid by ORS is highly effective and has saved countless lives. ORS takes advantage of a co-transport mechanism not affected by cholera toxin, wherein sodium (Na^+) moves across the gut mucosa along with actively transported glucose. Sodium losses in the stool in cholera are high, so that an oral replacement solution containing 90 mmol/L Na^+ is the WHO recommendation.
- Content of WHO ORS in grams (to be added to 1 litre of water)

NaCl	3.5
$NaHCO_3$	2.5
KCl	1.5
Glucose	20

- Rice-based ORS is also available. They contain rice powder instead of glucose. They have less osmolality, provide more nutritional benefits and may also reduce the amount of diarrheal stool, an effect not seen with ordinary ORS.

Intravenous Fluids

- Are necessary for the severely dehydrated. Ringer lactate is the best choice as it contains all the electrolytes. The total fluid deficit, which is usually estimated as 10% of body weight, can be infused within 4 hours and half of this within the first hour. Oral fluid can usually be substituted thereafter but patients with continued large-volume diarrhea require intravenous fluid until diarrhea stops. Hypokalemia may develop and can be corrected by potassium supplements. Fluid replacement is monitored by urine output.

Antibiotics

- Although not necessary for cure, the use of an antibiotic to which the organism is susceptible will diminish the duration and volume of fluid loss and will hasten clearance of the organism from the stool. Single-dose tetracycline (2 g) or doxycycline (300 mg) is effective in adults but is not recommended for children <8 years of age because of possible deposition in bone and developing teeth. Antibiotics can be continued for 3 to 5 days, though single dose is enough for most of the cases. In areas where tetracycline resistance is prevalent ciprofloxacin or erythromycin can be used for adults. For children, furazolidone has been the recommended agent and trimethoprim-sulfamethoxazole the second choice. Erythromycin is also a good choice for children.

Prevention

- Hygienic measures should be implemented. Avoid unboiled water, food from street vendors, raw or undercooked seafood, and raw vegetables. Water can be treated with chlorine or iodine, by filtration, or by boiling.

Antibiotic Prophylaxis

- Not routinely recommended. WHO recommends prophylaxis only if an average of one household member in a family of five becomes ill after the first case. Mass chemotherapy of entire communities is not effective and is not recommended.

Vaccines

- A killed vaccine is available which provides less than 50% protection for 3–6 months. It is given intramuscularly and causes adverse effects, including pain at the injection site, malaise, and fever. The vaccine's limited efficacy may be due to its failure to induce a local immunity at the intestinal mucosal surface.
- Two types of oral cholera vaccines are licensed for use in Europe. The *first is a killed whole-cell vaccine* given with the nontoxic B subunit of cholera toxin (rBS-WC). It provides ~70% protection over a 3-year period. WHO recommends that the oral rBS-WC vaccine should be considered for use in preventing cholera in populations at risk of an epidemic within six months and not experiencing a current epidemic. The *second one is a live attenuated vaccine*. It is associated with a significant increase in the titer of vibriocidal antibody in ~75% of recipients, including children, with almost no side effects. Unfortunately, in a large field trial in Indonesian children,

this vaccine failed to induce protection against clinical cholera. Other live attenuated vaccines are now undergoing clinical trials.

Q. Describe the etiology, epidemiology, pathogenesis, clinical features, diagnosis and management of plague.

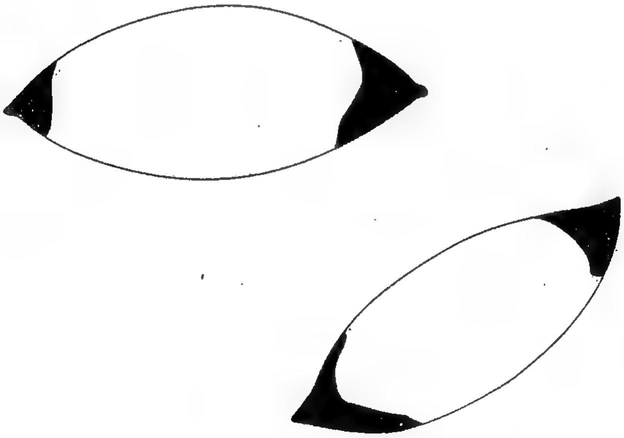

Fig. 1.6: Plague bacilli

Etiology

- Plague is an acute, febrile, zoonotic disease caused by infection with *Yersinia pestis*. *Yersinia* is named in honor of Alexander Yersin, who first isolated this bacterium.
- *Y. pestis* is a gram-negative coccobacillus in the family Enterobacteriaceae. It has bipolar staining pattern and appears like a safety pin.
- Plague is one of the most virulent and potentially lethal bacterial diseases known.

Epidemiology

- Foci of plague are present on most continents except Australia. Multiple stable foci exist in Africa, Asia, and South America.
- It has been known for many centuries. It was described as *Mahamari* in India. The latest outbreak occurred in India in 1994 and affected Maharashtra (earthquake-affected areas) and Surat of Gujarat.
- Low atmospheric temperature and humidity favour epidemics, which occur mostly from September to May.
- All the age groups and both sexes are affected.
- Plague is a zoonosis primarily affecting rodents. Humans are accidental hosts who play virtually no role in the maintenance of *Y. pestis* in the ecosystem.
- The reservoir of infection is *Rattus norvegicus* in Western countries. In India wild rats like *Tatera indica* and *Bandicota bengalensis varius* are the reservoirs of infection. Domestic rats get infected by coming in contact with wild rats. When domestic rats die or come in contact with the human population, the disease spreads. The chief vector of the disease is the flea *Xenopsylla cheopis*. Farmers, rat catchers and those who eat rats may contract plague from the wild reservoir. When fleas feast on dead rats they ingest plague bacilli which multiply and block proventricularis. This blocked flea inoculates the host and thus spreads the disease. Infection can also take place by the bite of a rat and by handling infected material. Pneumonic plague spreads from man to man by droplet infection. Dogs and cats can become infected with *Y. pestis* by eating infected rodents and possibly by being bitten by infective fleas. Both dogs and cats may transport infected fleas from rodent-infested areas to the home environment.

Pathogenesis

- *Y. pestis* is highly invasive and pathogenic. It produces many virulence factors and also a lipopolysaccharide endotoxin which is important in sepsis, triggering the systemic inflammatory response syndrome and its complications.
- *Y. pestis* organisms inoculated through the skin or mucous membranes are carried to regional lymph nodes via lymphatic channels, although direct bloodstream inoculation and dissemination may take place. Phagocytes, which can phagocytize *Y. pestis*, may play a role in dissemination of the infection to distant sites. Plague can involve almost any organ, and untreated plague generally results in widespread and massive tissue destruction. Infected lymph nodes (buboes) contain huge numbers of infectious plague organisms and show distorted or obliterated lymph node architecture with loss of vascular integrity, hemorrhage, necrosis, infiltration of neutrophils, and extensive serosanguineous effusion. Primary septicemic plague consists of sepsis in the absence of a bubo; secondary septicemic plague is a complication of bubonic or pneumonic plague. DIC can occur in severe cases. Vascular damage may lead to widespread ecchymoses and petechiae. Acral ischemia and gangrene may sometimes develop.
- Primary plague pneumonia is lobar or multilobar. Secondary plague pneumonia begins more diffusely. The affected lung tissue is characterized by edema, hemorrhagic necrosis, and infiltration by neutrophilic leukocytes.

Clinical Features

- Incubation period is 2–8 days.
- There is rapid onset of fever associated with headache, backache and bodyache. If not treated early, plague can follow a toxic course, resulting in shock, multiple-organ failure, and death.

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- In humans, plague presents mainly as three forms; bubonic, septicemic, and pneumonic. Bubonic plague is most common type and is usually caused by the bite of an infected flea. Septicemic and pneumonic plague can be either primary or secondary to spread from other sites.

Bubonic Plague

- Initially patient experiences fever, chills, headache, myalgia and arthralgia. These symptoms are followed usually within 24 hours by pain and swelling in one or more regional lymph nodes proximal to the site of inoculation of the plague bacillus. Since most of the flea bites are on legs, femoral and inguinal nodes are most commonly involved; axillary and cervical nodes are next most commonly affected. Within hours, the enlarging bubo becomes painful and tender. The patient usually guards against palpation and limits movement, pressure, and stretch around the bubo. The surrounding tissue often becomes edematous, and the overlying skin may be erythematous, warm, and tense. At the site of flea bite, there may be a papule, pustule, or ulcer. The ulcer may be covered by an eschar.
- If treated early, bubonic plague usually responds quickly, with resolution of fever and other systemic manifestations. Without treatment, patients become increasingly toxic, and secondary plague sepsis may result in DIC, bleeding, shock, and multi-organ failure.

Septicemic Plague

- Here primary septicemia develops in the absence of a bubo. Septic patients often present with gastrointestinal symptoms like nausea, vomiting, diarrhea, and abdominal pain, which may be confused with some abdominal disease. If not treated early with appropriate antibiotics, septicemic plague can be fulminant and fatal. DIC may develop which will manifest as petechiae, ecchymoses, bleeding from puncture wounds and orifices, and gangrene of limbs. Shock may develop which manifests as refractory hypotension, renal shutdown, and obtundation. Acute respiratory distress syndrome (ARDS) can occur at any stage of septicemic plague.

Pneumonic Plague

- Pneumonic plague is often secondary to bacteremia in bubonic or septicemic plague. However, primary pneumonic plague can occur, being acquired from inhalation of *Y. pestis* from another patient or animal or laboratory specimens.
- Pneumonic plague develops more rapidly and is more fatal than other two forms. Incubation period is usually 3 to 5 days. The onset is often sudden, with fever, headache, bodyache, and weakness. Pulmonary signs, including tachypnea and dyspnea, cough with expectoration, and chest pain, usually start on the second day of illness. Respiratory failure may develop. Usually one lobe is involved in early stages and later on it may spread to other lobes and other lung also.

Rare Presentations

- Plague meningitis, plague pharyngitis, endophthalmitis, and lymphadenitis at multiple sites.

Diagnosis

- Plague should be suspected in any patient with fever and painful lymphadenopathy. Patient should be questioned about travel to areas of endemic disease, and potential exposure to animal or rodent vector.
- ***Culture and staining***: This will confirm the diagnosis. Blood, aspirates from buboes, sputum and CSF can all be cultured and stained with Wright-Giemsa or Wayson's stain. Wayson's stain demonstrates the typical bipolar staining, which resembles a "closed safety pin." Gram's stain shows small gram-negative coccobacilli.
- ***Serology***: Demonstration of antibodies supports the diagnosis.
- ***Rapid diagnostic tests***: A new rapid diagnostic test (RDT) capable of detecting F1 antigen of the *Y. pestis* within 15 minutes has been developed. This test holds considerable promise for rapid diagnosis of plague.
- ***Chest X-ray***: May show bronchopneumonia, consolidation, pleural effusions and hilar or mediastinal adenopathy.

Treatment

- Patients should be isolated.
- Streptomycin is considered the drug of choice. However, gentamicin has been shown to be equally efficacious, cheaper and easier to administer. Hence, in many places gentamicin has replaced streptomycin as the drug of choice. Other antibiotics which are effective include tetracycline, doxycycline (100 mg PO or IV twice daily), chloramphenicol, and trimethoprim-sulfamethoxazole (160/800 mg twice daily). Antibiotics should be given for 10 days.
- Antibiotics are given orally but can be given parenterally in critically ill patients and to patients who cannot tolerate oral medication. In general, antimicrobial treatment should be continued for 7 to 10 days or for at least 3 days after the patient has become afebrile and has made a clinical recovery. Patients initially given intravenous antibiotics may be switched to oral regimens upon clinical improvement.
- Chloramphenicol may be used to treat plague meningitis, pleuritis, endophthalmitis, and myocarditis because of

its superior tissue penetration; it is used alone or in combination with streptomycin or another first-line agent.

- Complications like DIC, ARDS, and sepsis require treatment as per standard guidelines.
- Buboes may require surgical drainage.

Prognosis

- If not treated, plague is fatal in >50% of cases of bubonic disease and in nearly all cases of septicemic and pneumonic disease. Prognosis has improved now with the availability of antibiotics.

Prevention

- Avoid exposure to live or dead rodents and use insect repellants in endemic areas.
- Face to face contacts of patients with known or suspected pneumonic plague should be provided chemoprophylaxis with doxycycline (100 mg two times daily for 2 to 3 weeks). In pregnant women and children under the age of 8, trimethoprim-sulfamethoxazole has been recommended for five to seven days. Ciprofloxacin is also effective.
- Vaccines are being tested.

Q. Describe the etiology, clinical features, diagnosis and treatment of melioidosis.

Etiology

- Melioidosis is an infectious disease caused by *Burkholderia pseudomallei* (previously known as *Pseudomonas pseudomallei*). It is a gram-negative organism showing bipolar staining (safety-pin appearance) like plague bacillus. It is found in the soil and stagnant waters of the tropical and subtropical regions of Asia and Australia.

Epidemiology

- Melioidosis is found predominantly in Asia, Australia, and China. It is rare in the United States.
- The routes of infection are through skin abrasions, by ingestion, and inhalation.
- Percutaneous inoculation during exposure to wet season soils or contaminated water is the predominant mode of acquiring the infection. Hence, majority of melioidosis cases occur in the monsoonal wet seasons.

Clinical Features

- Incubation period ranges from 1–20 days.
- Most infections are asymptomatic.
- Immunocompromised state such as diabetes mellitus, malignancies, chronic renal failure and cirrhosis of the liver predispose to infection.
- Patients present with acute or chronic fever. Most of the patients have multiple abscesses. Abscesses may be superficial (skin abscess) or deep (ileo-psoas, liver or splenic abscesses). Patients may also develop arthritis, pneumonitis, or pneumonia. Septicemia may occur in some patients which may cause death.

Pathology

- Initially lesions begin as granulomas resembling tuberculosis, with giant cells but without acid-fast bacilli. Later these lesions become microabscesses. Micro-abscesses enlarge to become big abscesses.

Diagnosis

- Melioidosis should be considered in patients with fever and multiple abscesses. Multiple abscesses, especially those in the liver or spleen, should alert the physician to the possibility of melioidosis.
- Confirmation of the diagnosis is by demonstration of typical safety pin shaped organisms in smear and culture of abscesses. Pus may occasionally be sterile; hence, repeated samples should be cultured. In severe cases, blood culture may be positive.

Treatment

- The drug of choice is ceftazidime or carbapenems such as imipenem or meropenem for a minimum of 2 weeks and preferably for 4 weeks. Thereafter, combination of chloramphenicol, TMP-SMX, and doxycycline or with the single agent amoxicillin/clavulanate is recommended for 6 weeks to 6 months to eradicate infection.
- Abscesses should be drained by surgical procedures.
- Untreated, the case fatality may be 90% or more.

Q. Cat-scratch disease.

- Cat-scratch disease is cuased by *Bartonella hensalae*, a gram-negative bacillus.
- It occurs throughout the world and is seen commonly in children.
- Domestic cat is the animal reservoir of this micro-organism. It is caused by scratch, bite, or lick of a cat and by close contact.
- Usually 3 to 5 days after exposure, patient develops a papule that later crusts. Still later tender regional lymphadenopathy develops. There may be mild fever and malaise. The lymphadenopathy persists for 3 to 5 weeks. Complications like meningitis, transverse myelitis, encephalitis, hepatitis and osteomyelitis can occur.

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- The involved lymph node reveals characteristic granulomatous inflammation with stellate necrosis.
- Cat-scratch disease is generally benign and self-limiting. Antibiotics are not required except in immunocompromised patients and patients with encephalitis or other serious manifestations. It can be treated with azithromycin or doxycycline.

Q. Trench fever.

Etiology

- Trench fever, also known as *5-day fever* or *quintan fever*, is a febrile illness caused by *Bartonella quintana*, a gram negative bacillus. It was first reported in soldiers hiding in trenches during World War I. Hence it was called trench fever.

Epidemiology

- Trench fever is seen worldwide. It is more common in the United States.
- *B. quintana* is transmitted from person to person by the human body louse.

Clinical Manifestations

- Trench fever is characterized by the sudden onset of fever, headache, bodyache, malaise, weight loss and aseptic meningitis.
- Some patients may have minimal symptoms.

Diagnosis

- The infection is diagnosed by finding *Bartonella quintana* in blood. In cultures it is slow to grow. The infection can also be detected serologically by demonstration of antibodies.

Treatment

- Gentamicin for 2 weeks plus doxycycline for 6 weeks.

Q. Describe the etiology, epidemiology, pathogenesis, clinical features, diagnosis, and treatment of brucellosis.

Etiology

- Brucellosis is a zoonotic infection transmitted to human beings from infected animals. It is also known as undulant, Mediterranean, or malta fever. It is called undulant fever because of its remittent character.
- It is caused by Brucella organisms which are small, nonmotile, gram-negative rods.
- There are many species of brucella. Out of these, *Brucella melitensis* is the commonest cause of disease in humans and is found in sheep, goats, and camels. *B. abortus* is usually acquired from cattle or buffalo. *B. suis* is usually acquired from swine. *B. canis* is commonly acquired from dogs.

Epidemiology

- Brucellosis occurs worldwide. The disease is more common in young persons and six times more common in men than in women.
- Human brucellosis is usually associated with occupational or domestic exposure to infected animals or their products.
- The route of entry is by ingestion or inhalation or through mucosal or percutaneous exposure.
- Farmers, shepherds, goatherds, veterinarians, and workers in slaughter houses and meat-processing plants are commonly exposed to infection. Laboratory workers handling cultures or infected samples are also at risk. Others may acquire the infection through consumption of contaminated foods. The most common food items implicated are dairy products like cheese, unpasteurized milk, and ice cream. Raw meat and cosmetic products have been reported to spread the infection rarely.
- Person-to-person transmission is extremely rare, as is transfer of infection by blood or tissue donation.

Pathology

- Exposure to infection generates both humoral and cell-mediated immune responses. Organisms taken up by macrophages and other mononuclear cells can get disseminated to different organs. Since the organism is intracellular, it is protected from antibiotics and antibodies. Cell mediated immunity plays an important role in clearing the infection. Activated macrophages can kill intracellular brucellae and can clear the infection. However, some immunity to reinfection is provided by serum immunoglobulin (Ig). Initially, IgM levels rise, followed by IgG titers.
- Granulomas may form but without caseation. Without treatment, granulomas tend to join and suppurate which can be a source of recurrent bacteraemia.

Clinical Features

- The incubation period varies from 1 week to several months.
- Acute or insidious onset of fever which is low or high grade, remittent or intermittent, with chills and sweats, without localising signs in most cases. Fever can be characteristically undulant, i.e. it may disappear and again appear. Fever can be associated with a relative bradycardia.

- Constitutional symptoms of brucellosis include anorexia, asthenia, fatigue, weakness, and malaise, and weight loss.
- Lymphadenopathy and splenomegaly in 50% of the cases
- Brucellosis is a multisystem disease and affects almost all the organs. The symptoms depend on the system involved. Many complications can also develop depending on the system involved (*see* Table 1.6).
- Prolonged fever with a history of contact with animals or animal products and without any specific diagnosis should arouse a suspicion of brucellosis.

Investigations

- The diagnosis of brucellosis is difficult to confirm because the organism is difficult to culture and secondly, even casual contact with infected animals may induce positive serological tests even in persons without disease.
- Routine biochemical tests are usually within normal limits, although sometimes LFTs may be elevated. Peripheral leukocyte counts are usually normal or low, with relative lymphocytosis. Mild anemia and thrombocytopenia may be present. ESR can be elevated.
- Blood, bone marrow and lymph node culture may grow organisms.
- Serologic tests: May demonstrate antibodies to brucella. In endemic areas agglutinin titers of ≥1:320 to 1:640 are considered diagnostic; in nonendemic areas, a titer of ≥1:160 is considered significant. Repetition of tests after 2 to 4 weeks may demonstrate a rising titer.

Table 1.6 Clinical features and complications of brucellosis

Organ system	Clinical manifestations and complications
Musculoskeletal system	Myalgia, arthralgias, low back pain, spine and joint pain, and, rarely osteomyelitis, suppurative arthritis
Hematologic	Hemolytic anemia, thrombocytopenia, pancytopenia
Nervous system	Depression, lethargy, dizziness, tinnitus, meningitis, encephalitis
Eyes	Visual disturbances, keratitis, uveitis, optic neuritis
Respiratory system	Cough, pneumonia, chronic pulmonary granuloma
CVS	Palpitations, endocarditis, myocarditis, cardiac failure
Genito-urinary system	Epididymitis, orchitis
GIT	Hepatosplenomegaly, diarrhea, cholecystitis, sub-diaphragmatic abscess

- Polymerase chain reaction (PCR) shows promise for the detection and rapid diagnosis of Brucella spp in human blood specimens.

Treatment

- At least two antibiotics should be used. Monotherapy is not recommended. The "gold standard" for the treatment of brucellosis in adults is intramuscular streptomycin together with doxycycline. The alternative regimen (current WHO recommendation) is rifampicin plus doxycycline for 6 weeks. For patients in whom tetracyclines are contraindicated (children, pregnant women) TMP-SMX (trimethoprim-sulphomethoxazole) can be used instead of tetracyclines.
- There is evidence that other aminoglycosides can be used instead of streptomycin, e.g. netilmicin or gentamicin.
- Surgery in cases of infection of prosthetic heart valves and prosthetic joints (replacement required). If abscesses develop, they need to be drained.

Prevention

- Live attenuated vaccine is available for use in animals but none is available for human beings. Using gloves and mask while handling animals, drinking pasteurized milk may protect against acquiring infection.

Q. Granuloma inguinale (donovanosis) (granuloma venereum).

- Donovanosis is a chronic, progressively destructive bacterial infection of the genital region. It is a sexually transmitted infection.

Etiology

- It is caused by a gram-negative intracellular bacterium, *Klebsiella granulomatis*. The organism responsible for granuloma inguinale was initially described by Donovan (hence known as donovanosis) and subsequently the bacterium was classified as *Calymmatobacterium granulomatis*. Later, it was found that the molecular structure of this organism was similar to *Klebsiella* species and presently it is named *Klebsiella granulomatis*. This organism is an intracellular parasite, has a capsule with bipolar staining, which gives it a 'safety pin' appearance.

Clinical Features

- Incubation period is 1 to 4 weeks.
- The primary lesion is papulonodular which erodes to produce bright-red ulcers with pearly rolled edges. Ulcer bleeds easily. Most lesions are present on or around the genitals. The leisons progress slowly and heal with fibrosis. There is no lymph node involvement.

- Extragenital lesions occur in some cases and may involve oral cavity, lips, and bones. Lesions in the inguinal region may resemble lymph nodes.
- Lesions may develop malignant transformation.

Diagnosis

- *Klebsiella granulomatis* is very difficult to culture because it is extremely fastidious.
- The easiest method to visualize the organism is via smears from the base of the ulcer. The organisms are seen within the cytoplasm of macrophages. They exhibit bipolar staining with safety-pin appearance, and are referred to as Donovan bodies.
- A diagnostic PCR test has been recently developed and can be used for the detection of *C. granulomatis*.
- Serologic tests are also available.

Treatment

- The recommended antibiotic for granuloma inguinale is either trimethoprim/sulfamethoxazole or doxycycline. Alternatives include ciprofloxacin, erythromycin, or azithromycin. Treatment is given for 3–5 weeks.

Q. Actinomycosis.

- Actinomycosis is a chronic suppurative granulomatous infection characterised by abscess formation and multiple draining sinuses. The main pathological feature is formation of purulent material containing granules with a yellow sulfur-like appearance (termed sulfur granules).

Etiology

- The disease is caused by actinomycetes bacteria. *Actinomyces israelli* is the commonest pathogen causing actinomycosis. Though actinomycetes resembles fungus, actually it is a bacterium. It is gram-positive, nonmotile, nonsporing, noncapsulated.

Pathogenesis

- Actinomyces are normal commensals in the mouth, colon and vagina.
- Entry into tissues happens when there is a breach of the mucous membrane or from aspiration into the lung.
- Infection spreads by direct extension to contiguous tissues. Hematogenous spread to distant areas, particularly to the bone and brain, can happen.
- The organisms form visible microcolonies in the tissues called grains (sulfur granules). Sulfur granules are in vivo matrix of bacteria, calcium phosphate, and host material.

Clinical Features

Cervicofacial Actinomycosis

- Most common type. Painful swelling in the angle of jaw is the usual initial symptom. The swelling is purplish, firmly indurated, and feels woody or lumpy (hence, also known as lumpy jaw). There can be multiple such swellings which break to the surface, forming multiple sinus tracts discharging pus with yellowish white granules. It may spread to tongue, salivary glands, thorax, cervical spine, cranial bones and brain.

Thoracic Actinomycosis

- Results from aspiration of pharyngeal contents or dental plaques into the lungs or spread from *cervicofacial* actinomycosis. Patients usually c/o mild fever and cough with expectoration. Sputum can be blood-stained. Multiple abscesses may develop in the lungs which may break open into the exterior through multiple discharging sinuses. X-rays show consolidation bilaterally in the lower lung fields.

Abdominal Actinomycosis

- Results from diseased appendix. It can involve any organ in the abdomen. The disease usually presents as an abscess or mass lesion that is often fixed to underlying tissue and mistaken for a tumor. Sinus tracts may form in the abdominal wall.

Pelvic Actinomycosis

- Involves uterus and cervix. It has become common with the use of intrauterine contraceptive devices.

CNS Actinomycosis

- Rare. Can present as meningitis or multiple brain abscesses.

Musculoskeletal and Soft-Tissue Actinomycosis

- Skin, subcutaneous tissue, muscle, and bone involved alone or in various combinations.
- Multiple cutaneous sinus tracts.

Disseminated Disease

- Multiple organ infections.
- Lungs and liver most commonly involved.
- *Presentation*: Multiple nodules mimicking disseminated cancer.

Diagnosis

- Microscopic identification of sulfur granules in pus or tissues. Sometimes granules may be visible to the naked eye.

- Sulfur granules may also be found in mycetoma. If any doubt is there, identification of actinomycetes by microscopy and culture of pus or tissue specimens will confirm the diagnosis. However, because these organisms are part of the normal flora, their identification in the absence of sulfur granules in sputum, bronchial washings, and cervicovaginal secretions is of a little significance.

Treatment

- Requires prolonged antibiotic therapy (6–12 months).
- Penicillin is the drug of choice; 10 to 20 million units intravenously daily for 2–6 weeks followed by oral penicillin or amoxicillin for 6–12 months.
- Erythromycin, tetracycline, clindamycin and lincomycin are alternatives.

Q. Nocardiosis.

- Nocardiosis is an acute, subacute, or chronic infectious disease that occurs in cutaneous, pulmonary, and disseminated forms.
- Members of the genus *Nocardia* are ubiquitous saprophytes in soil, decaying organic matter, and fresh and salt water. *Nocardia* organisms are branching, beaded, filamentous, gram-positive bacteria. They are weakly acid-fast except *Nocardia madurae* which is non-acid-fast.
- Reproduce by branching.
- *N. asteroids* and *N. brasiliensis* cause pulmonary infections, meningitis and brain abscess. *N. madurae* causes mycetoma.

Clinical Features

- Primary cutaneous nocardiosis can present in three clinical forms: (1) cutaneous infection, (2) lymphocutaneous infection and (3) subcutaneous infection. Cutaneous infection presents as ulceration, abscess, and cellulitis. Lymphocutaneous nocardiosis manifests as a nodule/ulcer at the site of injury, lymphangitis and regional lymphadenopathy. Subcutaneous infection (also known as mycetoma) presents as pus discharging sinuses which may contain yellow coloured granules.
- Pulmonary and disseminated disease occurs due to inhalation of nocardia. Pulmonary nocardiosis is usually seen as opportunistic infection in immunocompromised patients. Patients present with fever and cough with expectoration. X-ray shows lung infiltrates.
- Extrapulmonary infections commonly involve brain. Cerebral nocardiosis presents as space-occupying lesion. Purulent meningitis may result if an abscess ruptures into the ventricles.

Diagnosis

- Microscopy
- Culture of pus and tissue specimens for nocardia.

Treatment

- Long-term antibiotic therapy is required (at least 6 months). Sulfonamides are the drugs of choice for nocardiosis. Sulfadiazine or sulfisoxazole can be used. Trimethoprim-sulfamethoxazole (TMP-SMZ) is also effective. Additional or alternative parenteral therapies include carbapenems (imipenem or meropenem), third-generation cephalosporins (cefotaxime or ceftriaxone), and amikacin, alone or in combination. Combination therapy is recommended for serious infections.
- Treatment is given for at least six weeks following clinical recovery.

Q. Mycetoma (Madura foot or maduromycosis).

- Mycetoma is a chronic infection of the skin and subcutaneous tissue characterized by a triad of tumefaction, sinus tract formation, and grains (sulfur granules). It is also known as Madura foot because it was first described in the Indian town of Madura region in the mid-19th century.

Etiology

- Mycetoma is caused by filamentous bacteria (actinomycetoma) and true fungi (eumycetoma).
- Mycetoma caused by filamentous bacteria is termed actinomycetoma. These filamentous bacteria are *Nocardia* species such as *Nocardia brasiliensis, Nocardia madurae, and Actinomyces israelii.*
- Mycetoma caused by true fungi is termed eumycetoma. Eumycetoma can be caused by *Pseudallescheria boydii, Phialophora jeanselmei, Madurella mycetomi, Madurella grisea, Cephalosporium falciforme,* and *Cephalosporium recifei.*

Clinical Features

- Mycetoma commonly affects young adults, particularly males aged between 20 and 40 years, mostly in developing countries. People of low socioeconomic status and manual workers such as agriculturalists, laborers and herdsmen are commonly affected. Organisms enter the skin through minor trauma.
- Mycetoma is a chronic, deep, progressively destructive, and deforming infection of skin, subcutaneous tissues, bone, and muscle. Most of the cases involve foot but

any part of the body can be involved. It manifests as a tumor-like area of localized edema or massive enlargement, with erythema and multiple draining sinus tracts. In a typical case, a triad of tumefaction, sinus tract formation, and grains (sulfur granules) is seen. The color of the grains varies depending on the pathogen.

- Note that mycetoma is different from actinomycosis. *Actinomyces israelii* can cause both actinomycosis and mycetoma.

Investigations

- *Gram's stain* of secretions can show filamentous gram-positive bacteria or gram-negative fungi.
- *Biopsy*: Shows suppurative granulomas sorrounding characteristic grains in the subcutaneous tissue. Causative filamentous bacteria or fungi can be seen in Gram's stain.
- Culture of the secretions or biopsy specimens.

Treatment

- Differentiation between actinomycetoma caused by bacteria and eumycetoma caused by fungi is important because treatment is different for both.
- For actinomycetoma (caused by bacteria), surgical debridement followed by prolonged antibiotic therapy is required. A combination of antibiotics are used including trimethroprim-sulphamethoxazole, streptomycin, dapsone and rifampicin.
- For eumycetoma (caused by fungi), surgery followed by antifungal therapy (amphotericin-B or itraconazone or ketoconazole) is used.

Q. Discuss the etiology, epidemiology, pathogenesis, clinical features, diagnosis and treatment of leprosy (Hansen's disease).

- Leprosy (Hansen's disease) is a nonfatal, chronic infectious disease caused by *Mycobacterium leprae*. To minimize the prejudice against those with leprosy, the condition is also known as Hansen disease, named after GA who discovered *M. leprae*.
- First described in ancient Indian texts from the sixth century BC.
- Mainly affects skin, peripheral nervous system, upper respiratory tract, eyes, and testes.
- Associated with social stigma.

Etiology

- *Mycobacterium leprae* which is acid fast and obligate intracellular organism.
- The organism grows best at 27–30°C; therefore, skin lesions tend to develop in the cooler areas of the body, with sparing of the groin, axilla, and scalp.
- Cannot be cultured *in vitro*.

Epidemiology

- 99% of leprosy cases are found in Asia, Africa and Latin America. Highest number of cases are in India.
- Affects all age groups. Peak onset is in the second and third decades of life.
- Leprosy is associated with poverty and rural residence.
- Its incidence is not increased by AIDS unlike tuberculosis.
- There has been a dramatic decline in leprosy cases because of effective multi-drug therapy.

Pathogenesis

- Incubation period is long, 5–10 years.
- It spreads by droplet infection when an infectious (lepromatous) patient releases the organisms by coughing and sneezing. The organism enters the body through skin, mucous membranes of the respiratory tract and possibly the gut. The infectivity of the disease is low and large percent of people exposed to the infection do not get infected.
- Leprosy is a spectral disease with two polar forms; tuberculoid and lepromatous leprosy. Tuberculoid leprosy occurs in people with good immunity. Lepromatous leprosy occurs in people with low immunity. Between these forms lies a large group of patients described as the borderline group. In this group patients showing features closer to lepromatous leprosy are designated borderline lepromatous (BL) leprosy and those with features closer to tuberculoid form are designated as borderline tuberculoid (BT) leprosy; patients with features lying midway between the two are classified as borderline (BB) leprosy.

Clinical Features

Tuberculoid (TT) Leprosy

- Occurs in people who possess a high degree of cell mediated immunity.
- More often affects brown and black people.
- The skin lesions of tuberculoid leprosy are only one or a few hypopigmented macules or plaques that are sharply demarcated and hypoaesthetic. Lesions usually have erythematous or raised borders, and are devoid of sweat glands and hair follicles and thus are dry, scaly, and anhidrotic.

- The regional or local nerve is thickened and may be tender. Most commonly affected nerves are ulnar, posterior auricular, peroneal, and posterior tibial nerves.
- Histology of the lesions shows granulomatous infiltrate consisting of macrophages, lymphocytes and giant cells. The infiltrate is more prominent around the nerves and the skin appendages.
- Smears from lesions show absent or very few AFB.
- Lepromin test is positive in TT leprosy.

Lepromatosus (LL) Leprosy

- Occurs in people who have less cell mediated immunity.
- It more often affects White people.
- The skin lesions are multiple, bilaterally symmetrical, hypopigmented macules, plaques, nodules or diffuse skin infiltration. The margins are ill defined, and diffuse. Diffuse infiltration of facial skin gives rise to convoluted folds, which give the face a lion-like appearance (hence called 'leonine facies').
- Infiltration of eyebrows leads to loss of eyebrows, initially lateral third.
- Nose can get involved which can cause nasal bridge collapse and epistaxis. Nasal septum can get perforated.
- Patients with LL leprosy have late involvement of nerves which presents as distal symmetric peripheral neuropathy. Neural involvement predisposes to painless burns and trophic ulcers, deformities and resorbed digits of the hands and feet.
- Systemic involvement causes lymphadenopathy, hepatosplenomegaly, testicular involvement and gynaecomastia, and bacillaemia. Smears from lesions show a large number of bacilli. Lepromin test is negative in LL leprosy.
- The disease runs a slow and progressive course. Patients may die of intercurrent infections, renal failure or amyloidosis all of which are complications of leprosy.

Borderline Group

- In the BT form, the lesions show features closer to tuberculoid form of the disease. Lesions may be more or a tuberculoid lesion may have a satellite lesion close to it. In BL form, the lesions show features closer to the lepromatous form. Genuine borderline (BB) cases have features midway between tuberculoid and lepromatous leprosy.

Primary Neuritic Leprosy

- Here nerve involvement is seen without any skin lesions. Nerves are thickened and may be tender with associated loss of sensations. Facial palsy can also be a presentation.

Indeterminate Leprosy

- This is often a single hypopigmented macule which may be atrophic and may be hypoasthetic. Acid-fast bacilli may or may not be seen. At this stage it is difficult to tell which way the lesion will progress whether towards the lepromatous end or tuberculoid end.

Table 1.7 Differences between tuberculoid and lepromatous leprosy

Feature	Tuberculoid leprosy (TT)	Lepromatous leprosy (LL)
Skin lesions	Up to 3 in number; sharply defined asymmetric macules or plaques with tendency toward central clearing, elevated borders. Hypesthesia an early sign	Multiple symmetric lesions with ill-defined margins, multiple infiltrated nodules and plaques or diffuse infiltration; leonine facies and loss of eyebrows. Hypesthesia a late sign
Nerve lesions	Peripheral nerves involved early. Only a few nerves are involved. Nerves are thickened and may be tender	Nerves are involved late in the disease. Symmetric involvement common
Acid-fast bacilli (bacterial index)	0 to 1+	4 – 6+
Lymphocytes	3+	0 – 1+
Lepromin skin test	Positive	Negative
IgM antibodies to PGL-1	Found most often	Found less often

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Diagnosis

- Currently, the diagnosis of leprosy is based on clinical signs and symptoms. Examination of skin smears and/or biopsy can confirm the diagnosis.

Clinical Signs and Symptoms

- In an endemic country or area, an individual should be regarded as having leprosy if he or she has one of the following features:
- Hypopigmented or reddish skin lesion(s) with definite loss of sensation;
- Involvement of the peripheral nerves, as demonstrated by loss of sensation and weakness of the muscles of hands, feet or face;
- Skin smear positive for acid-fast bacilli.

Skin Smears and Biopsy

- Skin smears may be taken from lesions on the ears, elbows, and/or knees. A biopsy should be taken from entirely within a lesion.

Other Diagnostic Tests

- *Measurement of anti-phenolic glycolipid-1 (PGL-1) antibodies:* This is a specific serologic test based on the detection of antibodies to phenolic glycolipid-1. This test yields a sensitivity of 95% for the detection of lepromatous leprosy but only 30% for tuberculoid leprosy.
- *Polymerase chain reaction (PCR):* This can be used to identify the mycobacterium in biopsy samples, skin and nasal smears, and blood and tissue sections.
- *Lymphocyte migration inhibition test (LMIT):* As determined by a lymphocyte transformation and LMIT, cell-mediated immunity to *M. leprae* is absent in patients with lepromatous leprosy but present in those with tuberculoid leprosy.

Treatment of Leprosy

- There are 3 main drugs for the treatment of leprosy. These are dapsone, clofazimine, and rifampicin. Of these drugs, only rifampicin is bactericidal but dapsone is the most important.
- Other agents which are effective against leprosy are minocycline, ofloxacin and clarithromycin.
- WHO has made recommendations for the treatment of leprosy. For treatment purposes, the WHO classifies patients as paucibacillary and multibacillary. Previously, patients without demonstrable AFB in the dermis were classified as paucibacillary and those with AFB as multibacillary.
- Currently, most leprosy programmes classify and choose the appropriate regimen for a particular patient using clinical criteria, which uses the number of skin lesions and nerves involved to classify leprosy patients into paucibacillary single-lesion leprosy (one skin lesion), paucibacillary leprosy (2–5 skin lesions) and multibacillary leprosy (more than five skin lesions).
- When skin smears are available and are reliable, any patient with a positive skin smear, irrespective of the clinical picture, must be classified as multibacillary leprosy and treated with the regimen for multibacillary leprosy.
- The WHO recommends that paucibacillary adults be treated with 100 mg of dapsone daily and 600 mg of rifampicin monthly (supervised) for 6 months. For patients with single-lesion paucibacillary leprosy, the WHO recommends as an alternative a single dose of ROM (rifampin-600 mg, ofloxacin-400 mg, and minocycline-100 mg).
- Multibacillary adults should be treated with 100 mg of dapsone plus 50 mg of clofazimine daily (unsupervised) and with 600 mg of rifampicin plus 300 mg of clofazimine monthly (supervised). Originally, the WHO recommended that multibacillary patients be treated for 2 years or until smears became negative (generally in ~5 years). However, current WHO recommendation of duration of therapy is 1 year. While 1 year of treatment is enough for most cases, concern has been expressed that it is not sufficient for higher bacterial index (BI) cases.

Table 1.8 WHO treatment of leprosy

Form of leprosy	WHO recommended regimen (1982)
Paucibacillary (tuberculoid)	Dapsone (100 mg/d, unsupervised) *plus* rifampin (600 mg/month, supervised) for 6 months
Multibacillary (lepromatous)	Dapsone (100 mg/d) *plus* clofazimine (50 mg/d), unsupervised; *and* rifampin (600 mg) *plus* clofazimine (300 mg) monthly (supervised) for 1–2 years

Complications of Leprosy

- ***Extremities:*** Distal myopathy, claw hand, loss of digits, foot drop, trophic ulcers
- ***Nose:*** Destruction of nasal cartilage with resultant saddle nose deformity and anosmia, epistaxis.
- ***Eye:*** Corneal ulcerations and development of opacities due to loss of sensation of cornea. Uveitis due to direct bacterial invasion with consequent cataracts and glaucoma.

- *Testes*: *M. leprae* can invade testes and cause aspermia or hypospermia. Erythema nodosum leprosum can also cause orchitis.
- *Amyloidosis*: Secondary amyloidosis is a complication of LL leprosy.
- *Nerve abscesses*: Seen in TT and BT forms of leprosy and can cause rapid nerve destruction which may be permanent.

Q. Write briefly about antileprosy drugs.
(see Table 1.9)

Q. Lepra reactions.

- Lepra reactions are immunologically mediated inflammatory states. They occur due to abrupt change in immunological response of the body against *M. leprae*.
- They can cause considerable suffering to the patient and sometimes can be life threatening.
- Two types of reactions are usually seen.

Type I reaction (reversal reaction)

- Type I reactions occur in borderline forms of leprosy as a result of increased activity of the body's immune system against *M. leprae*. Usually the BL form changes to BT form with treatment due to increase in immunity, hence this type of reaction is also known as reversal reaction. Cell mediated immunity plays a major role here. It occurs both in paucibacillary and multibacillary leprosy.
- Manifestations include signs of inflammation in pre-existing lesions, appearance of new skin lesions, neuritis, and rarely fever. Ulnar nerve is usually affected at elbow, which may be painful and exquisitely tender. Foot drop may result due to peroneal nerve involvement. If patients with affected nerves are not treated promptly with steroids, irreversible nerve damage may occur.

Type 2 lepra reaction (erythema nodosum leprosum, ENL)

- Type 2 lepra reaction occur in patients with high load of leprosy bacilli as in multi-bacillary/infiltrative type of leprosy. Type-2 reaction can involve multiple organs and systems, causing generalized symptoms.
- It occurs when large numbers of leprosy bacilli are killed with release of their antigens. These antigens provoke an arthus type allergic reaction producing antigen antibody immune complex reaction (type III hypersensitivity) in the presence of complement system. Immune complexes are deposited in the tissues (skin, eyes, joints, lymph nodes, kidneys, liver, spleen, bone marrow, endothelium and testes) as well as in the circulation.

Table 1.9 Antileprosy drugs

Drug	Mechanism of action	Features	Dosage	Side effects
Dapsone	Inhibition of folic acid synthesis	Bacteriostatic. Inexpensive and relatively non-toxic	100 mg daily	Agranulocytosis hemolytic anemia in patients with G6PD deficiency
Rifampicin	Rifampicin binds the DNA-dependent RNA polymerase complex uncoupling transcription	Most bactericidal drug available for the treatment of leprosy	600 mg monthly	Renal failure, bone marrow suppression, "flu-like" syndrome, and hepatitis, induction of liver cytochrome 3A4
Clofazimine	Exact mechanism not known	Weakly bactericidal against *M. leprae*	50 mg daily	Skin pigmentation.
Ofloxacin	Interferes with bacterial DNA replication by inhibiting DNA gyrase	Bactericidal	400 mg single dose as part of ROM single dose regimen	Nausea, diarrhea and other gastrointestinal complaints CNS effects such as insomnia, headache, dizziness, nervousness, and hallucinations
Clarithromycin	Inhibits bacterial protein synthesis by binding to 50-S ribosomal subunit	Bactericidal for *M. leprae*	500 mg daily	Gastrointestinal irritation, nausea, vomiting, and diarrhea
Minocycline	Inhibits protein synthesis by binding to 30S ribo-somal subunit	*Bactericidal for M. leprae*	100 mg daily	Discoloration of teeth in infants or children

- Most cases of ENL follow the initiation of chemotherapy, usually within 2 years. Rarely it may occur even before the diagnosis of leprosy and may in fact point towards leprosy diagnosis.
- Patients usually present with multiple painful erythematous papules that resolve spontaneously in a few days but may recur. Patients may also have fever, arthritis, myalgia, epididymo-orchitis, iridocyclitis and lymphadenopathy. There can be anemia, leukocytosis, and abnormal liver function tests. Skin biopsy of erythematous papules reveals vasculitis or panniculitis. Rarely severe ENL can result in death.

Differences between Type 1 and Type 2 lepra reactions

Table 1.10 Differences between Type 1 and Type 2 lepra reactions

Type 1 reaction	Type 2 reaction
It occurs both in paucibacillary and multibacillary leprosy	Occurs mainly in multibacillary (lepromatous) leprosy
Occurs due to increase in cell mediated immunity (delayed type hypersensitivity)	Occurs due to antigen antibody (immune complex) deposition
Localised	More generalized
Skin lesions inflammation in pre-existing lesions, appearance of new skin lesions	Existing skin lesions remain unchanged and new red, painful, tender, cutaneous subcutaneous nodules appear (ENL)
Nerve involvement common	Uncommon
Little or no fever and other constitutional symptoms	Prominent fever and other constitutional symptoms
Eye involvement in the form of weakness of eyelid muscles leading to incomplete closure may occur (nerve involved)	Internal eye disease (iritis, iridocyclitis) occurs, lepromatous nodules are seen
Other organs not affected	Multiple organs may be affected

Lucio's Phenomenon

- This rare reaction is seen exclusively in patients of Caribbean and Mexican origin.
- It is seen with lepromatous leprosy. It affects most often those who are untreated.
- Patients develop recurrent, large, ulcerative lesions—particularly on the lower extremities. Ulcers may develop all over the body. Secondary infection and consequent sepsis can be fatal. Ulcers happen due to ischemic necrosis of skin, which in turn is due to thrombus formation in blood vessels supplying skin due to heavy parasitism of endothelial cells with AFB, and endothelial proliferation. Immune complex deposition may also play a role in thrombus formation.

Treatment of Lepra Reactions

- For mild type 1 lepra reaction, analgesics, such as acetylsalicylic acid or paracetamol are enough. For severe type 1 lepra reactions with evidence of neuritis (pain, loss of sensation or function), steroids such as oral prednisolone should be used. The usual dose of prednisolone is 40–60 mg daily (1 mg/kg) initially followed by a gradual tapering. The duration of steroid therapy is 12-week.
- Therapy for type 2 reaction includes analgesics, such as acetylsalicylic acid or paracetamol, and steroids (oral prednisolone). In patients with severe type 2 reactions, who do not respond to steroids or in whom steroids are contraindicated, *clofazimine* at high doses or *thalidomide* may be used under close medical supervision. Clofazimine often requires 4–6 weeks before an effect is seen, and therefore, initially it should be combined with steroids.

Q. Syphilis.

- Syphilis is an infectious venereal disease caused by the spirochete *Treponema pallidum*.
- It is characterized by episodes of active disease interrupted by periods of latency.

Etiology

- Syphilis is caused by pallidum subspecies of treponema pallidum which belongs to spirochete group.
- It is spiral in shape. Live organisms can only be seen under dark-ground illumination because of poor resolution with conventional light microscopy. Treponema organisms have characteristic to and fro, undulating, corkscrew-like and angulating movements.
- Syphilis is becoming a rare disease now after the discovery of penicillin. However, efforts to eradicate this disease have been unsuccessful.

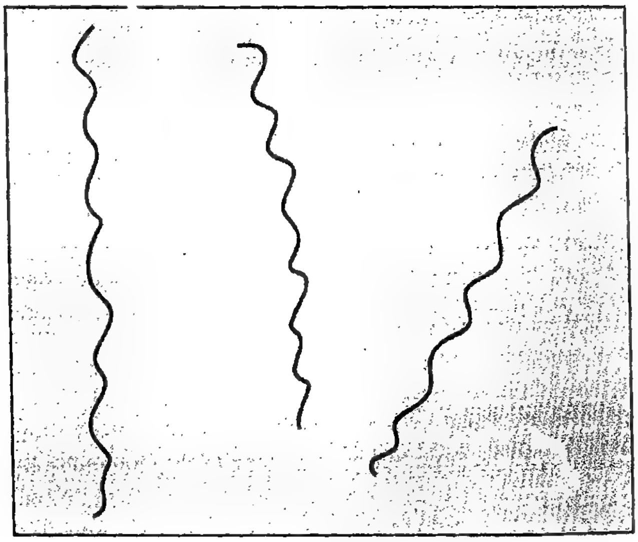

Fig. 1.7: *Treponema pallidum*

Pathophysiology

- The only known natural host for *T. pallidum* is man.
- Almost all cases of syphilis are acquired by sexual contact. Less commonly it is acquired by nonsexual personal contact, infection in utero (congenital syphilis), and blood transfusion. 1 in 2 persons exposed to infection gets infected.
- Syphilis is usually classified into 4 stages: Primary, secondary, latent, and tertiary. It can be acquired or congenital.
- *Primary syphilis*: In acquired syphilis, after exposure, *T. pallidum* penetrates intact mucous membranes or microscopic dermal abrasions and enters the lymphatics and blood to produce systemic infection. Primary syphilis is characterized by the development of a painless chancre at the site of entry after an incubation period of 3–6 weeks. The lesion has a punched-out base and rolled edges and is highly infectious. Histologically, the chancre is characterized by local inflammation with infiltration by macrophages and lymphocytes. In this stage, the spirochete can be isolated from the surface of the ulceration or the overlying exudate of the chancre. Whether treated or not, healing occurs with residual fibrosis.
- *Secondary syphilis* develops several weeks or months after the appearance of the primary lesion. During this stage, the spirochetes multiply and spread throughout the body. Secondary syphilis has numerous clinical manifestations. Common manifestations include malaise, fever, myalgias, arthralgias, lymphadenopathy, and rash.
- *Latent syphilis* is characterized by resolution of skin lesions and other clinical manifestations. However, serologic tests are positive for *T. pallidum*.
- *Tertiary or late syphilis* develops years after the initial infection (5–10 years later) and can involve any organ system. The most dreaded complications are neurosyphilis and involvement of the aortic valve and root. Initially syphilis mainly involves meninges and vasculature of CNS (meningovascular syphilis), later the parenchyma of brain and spinal cord is involved.
- Regardless of the stage of disease and location of lesions, histopathologic hallmarks of syphilis are endarteritis and a plasma cell-rich infiltrate. The syphilitic infiltrate is actually a delayed-type hypersensitivity response to *T. pallidum*, and can result in gummatous ulcerations and necrosis seen in tertiary syphilis. Antigens of *T. pallidum* induce treponemal antibodies and nonspecific reagin antibodies.

Clinical Features

- Acquired syphilis has predictable stages though there may not be clear cut demarcation between the stages. Four stages can usually be recognized and include *(1) primary, (2) secondary, (3) latent, and (4) tertiary* syphilis.

1. Primary Syphilis

- The typical lesion is a primary chancre which begins as a single painless papule that rapidly becomes eroded and usually becomes indurated. It has a firm consistency. In heterosexual men the chancre is usually located on the penis, whereas in homosexual men it is often found in the anal canal or rectum, in the mouth, or on the external genitalia. In women, it is usually found on the cervix and labia. Regional lymphadenopathy is usually seen. Lymph nodes are firm, nonsuppurative, and painless.

2. Secondary Syphilis

- Secondary syphilis has protean manifestations. These include skin and mucous membrane lesions and generalized painless lymphadenopathy. The healing primary chancre may be still present in some cases. The skin lesions are macular, papular, papulosquamous rashes, and occasionally pustules. The rashes may be very subtle and may be missed. Initial lesions are bilaterally symmetric, pale red or pink, nonpruritic, discrete, round macules that measure 5 to 10 mm in diameter and are distributed on the trunk and proximal extremities. After many days or weeks, red papular lesions appear. These lesions may progress to pustular lesions.
- In warm and moist areas like perianal area, vulva, scrotum etc, papules can enlarge and become eroded to produce moist, pink or gray-white, highly infectious lesions called condylomata lata. Mucosal lesions include erosions, called mucous patches and occur on lips, oral mucosa, tongue, palate, pharynx, vulva and vagina, glans penis. The mucous patch is painless with a red periphery.
- Constitutional symptoms may accompany secondary syphilis and include fever, weight loss, malaise, anorexia and headache. Meningitis can occur rarely.
- Less commonly there can be hepatitis, nephropathy, arthritis, periostitis, iritis and uveitis.

3. Latent Syphilis

- In latent syphilis serologic tests for syphilis are positive but there are no clinical manifestations. In latent syphilis *T. pallidum* is present in the body. Latent syphilis can get transmitted to the fetus in utero and to others through blood transfusion.

4. Tertiary Syphilis

- Tertiary syphilis is characterized by a persistent low-level burden of pathogens, against which a potent and self-destructive immune response is mounted. It is usually very slowly progressive and noninfectious. Any organ of the body may be involved, but three main types are: *neurosyphilis, cardiovascular syphilis* and *gummatous (late) syphilis.*

Neurosyphilis

- Traditionally, neurosyphilis was considered to be a late manifestation of syphilis, but this is not true and CNS can get affected anytime. CNS involvement can be asymptomatic or symptomatic. Asymptomatic neurosyphilis refers to patients without any neurological signs and symptoms but have CSF abnormalities or a positive VDRL test. Such asymptomatic patients should be treated because untreated patients may progress to symptomatic neurosyphilis.
- Neurosyphilis can be meningeal, meningovascular, and parenchymatous syphilis. The last category includes general paresis and tabes dorsalis. Meningeal syphilis occurs usually in <1 year after infection, meningovascular syphilis occurs 5 to 10 years after infection, general paresis after 20 years, and tabes dorsalis after 25 to 30 years.
- Meningeal syphilis presents with typical signs and symptoms of meningitis like headache, nausea, vomiting, neck stiffness, and alteration of mental status.
- Meningovascular syphilis involves meninges and also blood vessels leading to stroke.
- General paresis happens due to widespread brain parenchymal damage and includes abnormalities corresponding to the mnemonic PARESIS: *p*ersonality disturbances, *a*ffect abnormalities, *r*eflex hyperactivity, *e*ye abnormality (Argyll Robertson pupils), *s*ensorium changes, *i*ntellectual impairment and *s*lurred speech.
- In tabes dorsalis there is demyelination of the posterior columns, dorsal roots, and dorsal root ganglia. Symptoms include ataxic wide-based gait, paresthesia, bladder disturbances, impotence, areflexia and loss of joint position, deep pain, and temperature sensations. Argyll Robertson pupil can be seen in both tabes dorsalis and general paresis. It reacts to accommodation but not to light. Optic atrophy also occurs frequently in tabes.

Cardiovascular syphilis

- Cardiovascular manifestations are due to endarteritis obliterans of the vasa vasorum, which provide blood supply to large vessels. This results in weakening of tunic media and formation of aneurysm, aortitis (with linear calcification of the ascending aorta on chest X-ray), aortic regurgitation, or coronary ostial stenosis. Symptoms usually appear 10 to 40 years after infection. The most common finding on cardiovascular examination is a diastolic murmur with a tambour quality, secondary to aortic dilation with valvular insufficiency.

Gummatous syphilis (late syphilis)

- Gummas are nothing but areas of granulomatous inflammation with a central area of necrosis. Gummas may be single or multiple and size varies from microscopic to many centimeters. The most commonly involved sites are skin, mucous memebranes and skeletal system. Gummas of the skin produce painless and indurated nodular lesions which may break down to form punched-out ulcers with vertical edges. The ulcer heals in the middle with an atrophic tissue-paper scar and spreads peripherally. The base of the lesion is dull red and appears like 'wash-leather'. Nocturnal bone pain may occur due to bone involvement.

Congenital syphilis

- Transmission of *T. pallidum* from a syphilitic woman to her fetus across the placenta may occur at any stage of pregnancy, but the lesions in fetus develop after the fourth month of gestation.
- Treatment of the mother before 4th month of gestation can prevent fetal damage. Untreated maternal infection may lead to abortion, stillbirth, prematurity, neonatal death, or nonfatal congenital syphilis.
- Among infants born alive, congenital syphilis may or may not be clinically apparent.
- All women should be screened for syphilis in early pregnancy. In areas of high prevalence serologic screening should be repeated in the third trimester and at delivery.
- The manifestations of congenital syphilis can be divided into three types:
  - *Early manifestations:* Appear within the first 2 years of life. These are due to infection of various organs by *Treponema pallidum* and resemble secondary syphilis in the adult. These include rhinitis (snuffles), bullae (syphilitic pemphigus), vesicles, petechiae, papulosquamous lesions, mucous patches, and condylomata lata. The most common early manifestations are bone changes including osteochondritis, osteitis, and periostitis. Hepatosplenomegaly, lymphadenopathy and jaundice are also common.
  - *Late manifestations:* Appear after 2 years and are noninfectious manifestations. These include interstitial keratitis, eighth-nerve deafness, recurrent arthropathy and bilateral knee effusions known as Clutton's joints. Neurosyphilis and gummatous periostitis can also occur.
  - *Residual stigmata:* These include Hutchinson's teeth (centrally notched, widely spaced, peg-shaped upper central incisors) and "mulberry" molars (molars with multiple, poorly developed cusps). There can be abnormal facies like frontal bossing, saddle nose, and poorly developed maxillae. Saber shins, characterized by anterior tibial bowing, are rare. Rhagades are linear scars at the angles of the mouth and are caused by healing of early facial eruption.

Diagnosis

- The diagnosis of syphilis is suspected based on history and clinical features. Since the clinical features are protean, lab confirmation of diagnosis is required.

Dark Field Microscopy

- This is the most specific technique for diagnosing syphilis and can demonstrate *Treponema pallidum* in samples taken from chancre and condylomata lata. But dark field microscopy is not widely available.

Non-treponemal Tests

- These include Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test.
- Syphilitic infection leads to the production of non-specific antibodies that react to cardiolipin. This reaction is the basis of VDRL and rapid plasma reagin (RPR) test. Nontreponemal tests are widely used for syphilis screening.
- With nontreponemal tests, false-positive reactions can occur because of pregnancy, autoimmune disorders, and other infections. In addition, these tests may show a "prozone" phenomenon in which large amounts of antibody block the antibody–antigen reaction, causing a false-negative test in the undiluted sample.
- These tests may be negative in early primary syphilis and late syphilis in up to one-third of patients.
- After adequate treatment of syphilis, nontreponemal tests eventually become nonreactive.
- Titers are not interchangeable between different test types. Hence, the same nontreponemal test should be used for follow-up evaluations.

Treponemal-specific Tests

- Treponemal-specific tests detect antibodies to antigenic components of *T. pallidum*. These tests are used primarily to confirm the diagnosis of syphilis in patients with a reactive nontreponemal test.
- Treponemal-specific tests include the EIA for anti-treponemal IgG, the *T. pallidum* hemagglutination (TPHA) test, the microhemagglutination test with *T. pallidum* antigen, and the fluorescent treponemal antibody-absorption test (FTA-ABS).
- Unlike nontreponemal tests, which show a decline in titers or become nonreactive with effective treatment, treponemal-specific tests usually remain reactive for life. Therefore, treponemal-specific test titers are not useful for assessing treatment efficacy.

Treatment

- ***Primary syphilis*:** The treatment of choice is parenteral long-acting penicillin such as benzathine penicillin, given in a single dose of 2.4 million units in equally divided portions in each buttock deep IM. For penicillin allergic patients doxycycline 100 mg BD for 1 month should be given. Doxycycline is contraindicated in pregnant women and children. In such cases penicillin should be administered after desensitization. Ceftriaxone 1 gm daily IM/IV for 8 to 10 days is an alternative. At six and 12 months after treatment, patients with primary syphilis should be reexamined and undergo repeat serologic testing.
- ***Secondary syphilis*:** Treatment and follow up is same as primary syphilis.
- ***Latent syphilis*:** Early latent syphilis is treated in the same way as primary and secondary syphilis. Late latent syphilis is treated with 2.4 million units of benzathine penicillin given IM once a week for three weeks. Alternative regimens in patients with penicillin allergy include doxycycline, 100 mg BD for four weeks.
- ***Tertiary syphilis*:** Treatment for gummatous and cardiovascular syphilis is the same as that of late latent syphilis. Neurosyphilis should be treated with intravenous penicillin G (3 to 4 million units IV Q4h for 10 to 14 days) followed by benzathine penicillin 2.5 million units deep IM once a week for 3 weeks. Cetriaxone 2 gm daily IV or IM for 10–14 days is an alternative.
- ***Congenital syphilis*:** A single dose of 50,000 units of penicillin per kg should be given.

Q. VDRL (Venereal Disease Research Laboratory) test.

- VDRL is a nontreponemal antibody test to diagnose syphilis. It is quite sensitive but not very specific for syphilis. VDRL is reactive in 78 percent of patients with primary syphilis. It becomes positive within four to six weeks after infection or one to three weeks after the appearance of the primary lesion. Thus, these tests can be negative in early syphilis, when patients have lesions. VDRL can also be negative in some untreated patients in late syphilis. Hence, VDRL cannot be relied on for diagnosis in very early or late stage of syphilis.
- False positive VDRL test can occur in infections (TB, HIV, Lyme disease, infectious mononucleosis, malaria), pregnancy, connective tissue diseases, liver disease, and malignancy.
- Because of frequent false positive and false negative VDRL test, all positive tests and all negative tests in patients in whom syphilis is strongly suspected clinically, should be verified by a specific treponemal test.

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- The nontreponemal tests are quite useful for monitoring the patient's response to treatment, because the titers reflect disease activity. When these tests are used for this purpose, it is important to use the same test (either VDRL or RPR) for serial measurements because the two tests can differ significantly in their titers. When possible, it is also recommended that the same laboratory be used.

Q. Yaws.

- Yaws is a chronic, relapsing, nonvenereal infection caused by *Treponema pallidum pertenue*. Yaws, endemic syphilis (bejel), and pinta collectively constitute the endemic treponematoses.

Clinical Features

- The incubation period is 9 to 90 days (average 20 days).
- It predominantly affects children with peak incidence between 5 and 9 years of age.
- It spreads through close contact and the presence of minor skin lesions, abrasions and scratches which facilitate penetration and infection by the treponemae.
- Initially patient develops constitutional symptoms like bodyache, malaise and fever with rigors for a week. Then the initial yaws may start as a maculopapular eruption and then may develop into a papilloma. Initial lesions usually appears on the leg. Several weeks to months later generalised papillomatous eruptions may appear. Bone and joints can get affected and take the form of periostitis and osteitis. Gondou is a hypertrophic osteitis of the nasal process of the maxilla. Hyperkeratosis of soles and palms develops late. In late stages highly destructive ulcers may develop in the skin, bones and cartilages.
- Gangosa is the result of extensive destruction of nasal bones and cartilages. In severe cases, the whole of the palate may be destroyed, so that the nose and the mouth become one space.

Investigations

- Dark field microscopy of the specimens from early lesions may show spirochaetes.
- Serological tests are similar to those of syphilis (VDRL, RPR, FTA-ABS, etc.) and become positive at an early stage of infection, but tend to become negative later. Serological tests cannot differentiate yaws from other treponemal infections.

Treatment

- Benzathine penicillin is the drug of choice.
- The recommended dose is 6 lakh units for those under 10 years of age, and 12 lakh units for those above 10 years of age.
- In patients allergic to penicillin, tetracycline or doxycycline can be used.

Q. Pinta.

Etiology

- Pinta is an endemic treponematosis caused by *Treponema carateum.*
- Pinta is a Spanish word used to describe a spotted or mottled appearance. The lesions of pinta have a peculiar pigmented appearance on the skin.
- Transmission is nonvenereal by contact with skin lesions. Various biting and sucking arthropods have also been implicated.

Clinical Features

- It is predominantly a disease of childhood. After infection, 2–3 weeks later, a primary lesion at the site of inoculation appears. Secondary lesions appear after a month or a year. These secondary lesions are erythematous papules which become scaly and pigmented. These lesions gradually regress and become depigmented. Lesions are found mainly on distal extremities. Trunk and face may also be involved. The lesions have to be differentiated from other depigmented lesions like leprosy, yaws, syphilis, psoriasis, tinea versicolor and plain vitiligo or leucoderma.

Investigations

- Same as those described under yaws.

Management

- Penicillin is the drug of choice. Tetracycline or doxycycline are alternatives.

Q. Leptrospirosis.

Q. Weil's syndrome.

Etiology

- Leptospirosis is an infectious disease of humans and animals that is caused by pathogenic spirochetes of the genus *Leptospira*. It is considered the most common zoonosis in the world.
- Leptospira are coiled, thin, highly motile spirochaetes.
- Human infection is caused by *L. icterohaemorrhagica*, *L. canicola* and *L. hardjo* serotypes.

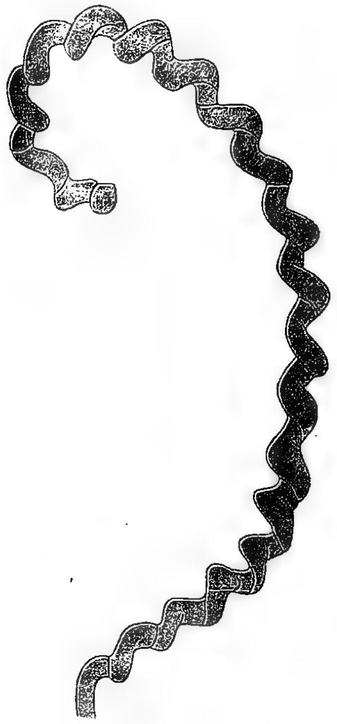

Fig. 1.8: Leptospira

Epidemiology

- It is a zoonosis and the reservoir of infection is rats *(L. icterohaemorrhagica)*, dogs (*L. canicola)* and pigs *(L. hardjo)*, respectively. These animals shed spirochaetes in the urine.
- Infection occurs by direct contact with urine or blood of an infected animal or by indirect contact with contaminated water, soil or vegetables. Human-to-human transmission is rare.
- The organism enters the body through cuts, mucous membrane or even unabraded skin.
- The disease is more common in veterinary personnel, agricultural workers, sewers, slaughter house workers and fishermen.

Pathogenesis

- The organism spreads through the blood stream to all organs. Multiplication takes place in blood and in tissues.
- Leptospires damage the wall of small blood vessels leading to vasculitis. Vasculitis causes leakage of plasma, hemorrhage and volume depletion. Vasculitis is responsible for most of the manifestations of leptospirosis.
- Although any organ may be involved, kidneys and liver are involved mainly. Kidney involvement leads to renal failure and oliguria. Liver involvement leads to jaundice and other liver function abnormalities. Muscle involvement leads to prominent myalgia and elevated CK levels. Lung involvement can lead to ARDS and pulmonary hemorrhage.
- Meningitis can develop when there is rise in antibody titers. This association suggests that an immunologic mechanism may be responsible for meningitis.

Clinical Features

- The incubation period varies from 2 to 20 days.
- More than 90% of patients have mild and anicteric form of leptospirosis.
- Severe leptospirosis with deep jaundice (Weil's syndrome) develops in 5 to 10% of patients.
- Leptospirosis has an acute leptospiremic phase followed by an immune leptospiruric phase. The distinction between the first and second phases is not always clear, and mild cases may not have the second phase.

Anicteric Leptospirosis

- Leptospirosis may present as an acute influenza-like illness, with fever, chills, severe headache, nausea, vomiting, and myalgias.
- Muscle pain is an important clinical feature.
- Headache may be intense.
- Physical examination shows fever, conjunctival suffusion, muscle tenderness, and hepatosplenomegaly. Mild jaundice may be present. Sometimes a rash also may be noted.
- After a gap of 1 to 3 days, fever recurs (second phase) in many cases. This second phase coincides with the development of antibodies (immune phase). Fever and myalgias may be less severe in the second phase. Aseptic meningitis, iridocyclitis and uveitis may develop during the second phase. Death is rare in anicteric leptospirosis.
- Most patients become asymptomatic within a week.

Severe Leptospirosis (Weil's Syndrome)

- Weil's syndrome, the most severe form of leptospirosis, is characterized by jaundice, renal failure, hemorrhagic tendency, and a high mortality rate.
- It is most often caused by leptospira icterohaemorrhagica serogroup.
- Initially symptoms are same as that of anicteric leptospirosis. However, later, jaundice, renal and vascular dysfunction develops. A biphasic pattern seen in anicteric leptospirosis is not seen in Weil's disease. The jaundice is very deep and gives an orange tinge to the skin. Tender hepatomegaly is usually present. Splenomegaly may also be present.
- Dialysis may be required for renal failure. Renal function usually recovers completely with treatment.
- Pulmonary involvement occurs frequently and results in cough, dyspnea, hemoptysis and rarely respiratory failure.

- Hemorrhagic manifestations include epistaxis, petechiae, purpura, and ecchymoses. Severe GI bleeding and adrenal or subarachnoid hemorrhage occur rarely.
- Complications of Weil's disease include rhabdomyolysis, myocarditis, pericarditis, congestive heart failure, cardiogenic shock, ARDS, necrotizing pancreatitis, septic shock and multiorgan failure.

Laboratory Features

Presumptive Diagnosis

- A positive result of a rapid screening test such as IgM ELISA, latex agglutination test, lateral flow, dipstick etc.

Confirmatory Diagnosis

- Isolation of pathogenic leptospires through culture of blood or other clinical samples.
- A positive PCR result (primarily for blood and serum in the early stages of infection).
- Fourfold or greater rise in titre or seroconversion in microscopic agglutination test (MAT) on paired samples obtained at least 2 weeks apart.

Other Tests

- Blood examination shows anemia, increased WBCs, decreased platelet count, and high ESR.
- LFTs show elevated direct bilirubin, elevated AST and ALT and prolonged prothrombin time.
- RFT (renal function tests) show elevated blood urea and creatinine.
- CK levels are high due to muscle damage.
- Urine examination may show proteinuria, RBCs, and cellular and granular casts.
- ECG may show low voltage, prolonged QT and non-specific ST and T wave changes.
- Chest X-ray may show patchy bronchopneumonia or ARDS.

Differential Diagnosis

- Leptospirosis should be differentiated from other febrile illnesses associated with headache, muscle pain and jaundice, such as dengue, severe malaria, enteric fever, viral hepatitis, hantavirus infections, sepsis and rickettsial diseases.

Treatment

- *Crystalline penicillin* 15 lakh units IV qid daily for 7 days OR *ceftriaxone* 1 gm IV bd for 5 to 7 days is the drug of choice for severe cases. Mild cases can be treated with oral antibiotics such as ampicillin, amoxicillin, erythromycin and doxycycline.
- Fluid and electrolyte balance should be maintained and supportive measures provided.
- Dialysis may be required for renal failure.

Q. Relapsing fever.

- The condition is so named because it is characterized by recurring fevers separated by afebrile periods.
- Relapsing fever is endemic in Africa, India, the Middle East and South America.

Etiology

- The infection is caused by various spirochete species of the *Borrelia* genus.
- Relapsing fever is an arthropod-borne infection spread by lice (*Pediculus humanis*) and ticks (*ornithodoros* species). Two main forms of this infection exist: tick-borne relapsing fever (TBRF) and louse-borne relapsing fever (LBRF).
- TBRF is caused by many *Borrelia* species (e.g. *Borrelia hermsii, Borrelia duttonii, etc.*), while LBRF is caused solely by *Borrelia recurrentis*.

Clinical Features

- After an incubation period of 7–10 days, the illness starts with high grade fever with chills and rigors, headache, bodyache and joint pains. There can be nausea, vomiting and sleeplessness. Patients may also develop a generalized petechial or ecchymotic rash, hepatosplenomegaly, jaundice, hemorrhagic tendency and hemoptysis. Meningitis can occur rarely.
- Although patients can completely recover from the initial stage, majority will develop one or more relapses. Louse-borne fever has more chances of relapse than tick borne fever. Relapses result from antigenic variation of the spirochete's outer-surface proteins.
- Untreated, one-third of patients may die.

Diagnosis

- Diagnosis can be confirmed by direct observation of spirochetes in peripheral blood smears during episodes of fever.
- Direct or immunofluorescence staining may also be used to visualize spirochetes using a fluorescence microscope.
- Motile spirochetes can be seen when specimens are examined by dark field microscopy.

Treatment

- Treatment with doxycycline (or tetracycline), erythromycin, or chloramphenicol is effective. For children <8 years of age and for pregnant women, erythromycin or penicillin is preferred, because of side effects of tetracyclines.

- A severe Jarish-Herxheimer reaction may occur after antibiotics are given and should be carefully watched for.
- Public health measures are needed to control the louse and tick populations.

Q. Rat-bite fever.

- Two organisms, *Spirillum minus* and *Streptobacillus moniliformis* can cause rat bite fever. Both are spirochetes.
- Human cases occur as a result of a bite or scratch (direct contact) from an infected rat. Infection may also occur from exposure to infected rat urine or by eating food or water contaminated with rat feces.
- Patient develops fever, inflammation, ulceration at the bite site, and regional lymphadenopathy. Arthritis and periodic fever can occur for several weeks.
- Diagnosis is by demonstration of spirochete in fluid from the ulcer, lymph node, or joint effusion.
- Treatment is by penicillin or tetracycline.

Q. Lyme disease (lyme borreliosis).

Q. Erythema migrans.

Etiology

- Lyme disease is a zoonosis caused by the spirochete *Borrelia burgdorferi.*

Epidemiology

- The disease is transmitted by the bite of the *Ixodes tick* which normally infects dogs, deer and sheep.
- The disease is seen mainly in western countries.
- Most cases occur in summer months in rural areas. Children and women are affected more commonly.

Clinical Features

Localized Infection (Stage 1)

- Borrelia organisms are injected into the skin when a tick bites.
- From the injected site, the spirochaete migrates outwards, producing a red macule or papule that expands slowly to form a large annular lesion called *erythema migrans (EM)* which is the characteristic rash of Lyme disease. As the lesion increases in size, it develops a bright red outer border and central clearing. Without therapy, EM typically fades within 3–4 weeks. EM usually is round or oval, but can be triangular or linear. Often, a central punctum is present at the bite site. EM enlarges by a few centimeters per day; single lesions typically achieve a diameter of approximately 5–6 inches. Since ticks tend to bite the areas where natural barriers impede their forward motion, rash location is usually on the popliteal fossa, axillary or gluteal folds, areas near elastic bands in bra straps or underwear. In children, the scalp, face, and hairline are especially common locations. Some patients with EM may have secondary EM lesions due to hematogenous spread. These lesions generally are smaller than the primary one, lack the central punctum, and tend to be more uniform in morphology than the primary lesion. Location of secondary lesions can be anywhere.
- Fever, chills, and malaise are also present in this stage.

Disseminated Infection (Stage 2)

- From the local site, organisms spread hematogenously to many sites within days or weeks after the onset of erythema migrans. Patients have severe headache, neck stiffness, fever with chills, arthralgias, and fatigue.
- One or more organ systems become involved as hematologic or lymphatic spread disseminates spirochetes to distant sites. Musculoskeletal (arthritis) and neurologic symptoms are the most common. Neurologic manifestations include cranial nerve palsy especially facial nerve palsy (Bell's palsy), meningitis and encephalopathy. Cardiac involvement presents as dizziness, syncope, dyspnea, chest pain, and palpitations.

Persistent Infection (Stage 3)

- After months or years of latency the articular (oligoarticular arthritis in large joints), neurological (polyneuropathy, encephalopathy) or dermatological (Acrodermatitis chronica atrophica) symptoms occur. Lyme arthritis is the hallmark of stage 3 Lyme disease. It tends to involve large joints (knee is involved in 90% of cases).

Investigations

- Lyme disease is usually diagnosed by the clinical features with serologic confirmation by testing for serum antibodies. The most frequently used test is the enzyme immunoassay (EIA) or enzyme-linked immunosorbent assay (ELISA). However, there are many limitations to serological tests. Thirty percent of acute cases are sero-negative; positive tests may reflect past rather than current infection.
- PCR testing of joint fluid is helpful in arthritis.
- More sophisticated immunological tests are being developed.

Management

- *B. burgdorferi* is sensitive to beta-lactam antibiotics (penicillins and cephalosporins) and to the tetracyclines. For severe cases, IV benzylpenicillin or ceftriaxone is given. For less severe cases oral doxycycline or amoxycillin for 3 weeks is effective.

Q. Epidemic typhus fever.

- Typhus refers to a group of infectious diseases that are caused by rickettsial organisms and that result in an acute febrile illness. Arthropod vectors transmit the etiologic agents to humans. The principle diseases of this group are epidemic or louse-borne typhus and its recrudescent form known as Brill-Zinsser disease, murine typhus, and scrub typhus.
- Epidemic typhus is the prototypical infection of the typhus group of diseases, and the pathophysiology of this illness is representative of all typhus fevers.
- Epidemic typhus is caused by the organism *Rickettsia prowazekii.*

Transmission

- It is spread by the vector *Pediculus corporis* (*body louse*).
- Organisms enter through abraded skin or mucous membrane when an infected louse is crushed on the body surface.

Clinical Features

- Incubation period is ~1 week.
- Typhus is a multisystem vasculitis and may cause a wide array of clinical manifestations.
- There is abrupt onset of malaise, fever with chills and severe headache. Cough is noted frequently. There is severe generalized myalgia.
- A rash begins on the upper trunk, usually on the fifth day, and then becomes generalized, involving all of the body except the face, palms, and soles. Initially, rash is macular, then it becomes maculopapular, petechial, and confluent.
- Photophobia and conjunctival congestion are frequently present. The tongue may be dry and coated. Confusion and coma are common. Skin necrosis and digital gangrene may be seen in severe cases.
- Patients may also develop hemodynamic collapse, multiorgan involvement including renal failure.

Investigations

- Indirect immunofluorescence assay (IFA) or enzyme immunoassay (EIA) testing can be used to evaluate for a rise in the immunoglobulin M (IgM) antibody titer, which indicates an acute primary disease.
- The complement fixation (CF) test is a serological test that can be used to demonstrate which specific rickettsial organism is causing disease by detection of specific antibodies.

Treatment

- Chloramphenicol or doxycycline. Treatment is continued until the patient becomes afebrile. Intravenous therapy is indicated in very sick patients. Supportive treatment is provided as needed.

Q. Scrub typhus.

Etiology

- Scrub typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi* (previously called *Rickettsia tsutsugamushi*), an intracellular gram-negative bacterium.

Transmission of Infection

- Scrub typhus is found in areas with heavy scrub vegetation, e.g. where the forest is regrowing after being cleared and along river banks. Hence, it is called scrub typhus.
- Seen in India, Asia, Australia, New Guinea, and Pacific Islands.
- *O. tsutsugamushi* is present in trombiculid mites. The organism is transmitted to humans through the bite of larval stage of mite called chiggers. Infected chiggers feeds on animal hosts, mainly rodents and infect them. Human infection is acquired by accident.

Clinical Features

- The site of chigger bite is marked by an eschar and is accompanied by regional lymphadenopathy, which may later become generalised. Other clinical features are high fever, intense headache, diffuse myalgias, and, sometimes a rash. Severe infections may be complicated by interstitial pneumonia, pulmonary edema, congestive heart failure, circulatory collapse, and signs and symptoms of CNS dysfunction, including delirium, confusion, and seizures. Death may occur as a result of these complications, usually late in the second week of illness.

Investigations

- Weil-Felix OX-K strain agglutination test is the oldest test available. It is inexpensive, but lacks specificity and sensitivity.
- Demonstration of antibodies against *Orientia tsutsugamushi* using indirect fluorescent antibody (IFA) test or indirect immunoperoxidase (IIP) test. IFA is the gold standard test. These tests are more sensitive and specific than Weil-Felix.

- Molecular detection using polymerase chain reaction (PCR) is possible from skin rash biopsies, lymph node biopsies or blood.

Treatment

- Drug of choice is doxycycline (100 mg bid PO for 7–15 days). Alternative is chloramphenicol 500 mg qid PO for 7–15 days.

Q. Q fever.

- Q fever is so named because when an outbreak occurred in Australia, it was unknown what type of fever it was. Hence it was named as Q (for query) fever. But later the micro-organism responsible for Q fever was isolated.
- Q fever is caused by infection with *Coxiella burnetii*, a small gram-negative micro-organism.
- Q fever is a zoonotic disease found in wild (mammals, birds, and ticks) and domestic animals (cattle, sheep, and goats).
- It is transmitted among animals by ticks. Infected animals shed it through their milk and conceptional products during delivery into soil.
- Human disease is acquired by inhalation of infected dust, handling infected animals, and by drinking contaminated milk. Veterinarians are at increased risk of infection. It can also be acquired through blood transfusion.

Clinical Features

- The incubation period is 3 to 30 days.
- It presents as flu-like illness with moderate fever, headache, myalgia, malaise and anorexia.
- Multiorgan involvement leads to pneumonia, hepatitis, pericarditis, myocarditis, endocarditis and meningo-encephalitis. Endocarditis commonly affects aortic valve with large vegetations present on 2D echo.

Diagnosis

- *Polymerase chain reaction (PCR)* of whole blood or serum can be used for rapid diagnosis.
- *Serologic methods*: Indirect immunofluorescence (IIF) (method of choice), complement fixation and enzyme-linked immunosorbent assay (ELISA). A fourfold increase in IgG antibody titer by immunofluorescent assay (IFA) of paired acute and convalescent specimens is the diagnostic gold standard to confirm diagnosis of Q fever.
- *Immunohistochemistry or culture* of affected tissue can provide definitive confirmation of infection by *Coxiella burnetii.*

Treatment

- Chloramphenicol and tetracyclines (doxycycline) are effective against Q fever.
- In pregnancy, trimethoprim-sulfamethoxazole is recommended for treatment.
- Quinolones are also effective.

Q. Psittacosis (ornithosis).

- Psittacosis, also known as parrot fever, is caused by *Chlamydophila* (formerly *Chlamydia*) *Psittaci.*
- Many birds are known to harbour the organisms, but psittacine species (parrots), poultry, and pigeons are the main sources of human infection.
- Organisms are transmitted to humans through contact with infected animals or birds or their fecal materials. Organisms enter human body through inhalation. It is common among pet bird (pigeon and parrot) owners and poultry (chicken and duck) farmers.

Clinical Features

- H/o bird contact present. Incubation period is 1 to 2 weeks. It presents as atypical pneumonia with fever and high respiratory rate. Examination may show relative bradycardia. Chest examination may show crepitations and signs of consolidation. Lung lesions are more extensive than the clinical features suggest. Respiratory failure can occur.
- Rarely extrapulmonary complications can occur and include myocarditis, encephalitis, meningitis, pancreatitis, glomerulonephritis, and disseminated intravascular coagulation.

Diagnosis

- Serological methods are preferred. These include complement fixation (CF), microimmunofluorescent antibody test (MIF), and monoclonal antibody techniques.
- PCR methods are under investigation.
- X-ray reveals patchy shadows, most often in the lower lobes.

Treatment

- Oral doxycycline 100 mg twice daily for 21 days is curative.
- Erythromycin is the second line therapy when tetracyclines are contraindicated.

Q. Lymphogranuloma venereum (LGV).

- LGV is a sexually transmitted disease caused by *C. trachomatis.*

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- The peak incidence of LGV corresponds to the age of greatest sexual activity: the second and third decades of life.

Clinical Features

- It is characterized by a painless genital lesion with bilateral inguinal lymphadenopathy (buboes).
- These buboes may break down to form multiple discharging sinuses with extensive scarring.
- In females, as the genital area drains into perirectal lymph nodes, early symptoms can be due to proctitis.
- Anal intercourse may lead to hemorrhagic proctitis with regional lymphadenopathy.
- Systemic symptoms like fever and leukocytosis are seen. Meningoencephalitis can develop rarely.
- Genital elephantiasis, strictures, urethral and rectal fistulas may occur as a late complication.

Diagnosis

- Direct microscopic examination of tissue scrapings shows typical intracytoplasmic inclusions or elementary bodies
- Isolation of the organism in cell culture
- Detection of chlamydial antigens or antibody in serum or in local secretions.

Treatment

- Recommended treatment is doxycycline 100 mg bd for 21 days. Macrolides (erythromycin or azithromycin) are alternatives.
- Surgical drainage for suppurative bubo may be required.

Q. Trachoma.

- Trachoma is a chronic conjunctivitis caused by *C. trachomatis*.

Epidemiology

- It is one of the most common causes of blindness in the world and is found in the tropics and the Middle East.
- It spreads by direct transmission and by flies. Trachoma may also occur in the neonate as it passes through the infected female genital tract.

Clinical Features

- It mainly affects children. Infection is bilateral and begins in the conjunctiva, with marked inflammation and scarring. Conjunctival scarring distorts the eyelids, causing them to turn inward so that the inturned lashes constantly abrade the eyeball (trichiasis and entropion). The cornea becomes involved, with inflammatory leukocytic infiltrations and superficial vascularization (pannus formation). Cornea may ulcerate, with subsequent corneal scarring and blindness.

Diagnosis

- Demonstration of intracytoplasmic chlamydial inclusion bodies in conjunctival smears.
- Chlamydial PCR is more sensitive and is often positive when smears or cultures are negative.

Treatment

- Application of tetracycline or erythromycin ointment to eyes for 2–3 months is effective.
- Systemic antibiotic therapy with oral tetracycline or sulphonamide or erythromycin is also effective.
- Surgery may be required for eyelid reconstruction and for treatment of corneal opacities.

Q. Influenza.

- Influenza is an acute respiratory illness caused by influenza viruses. Influenza viruses are encapsulated, single-stranded RNA viruses of the family orthomyxoviridae.

Epidemiology

- There are 3 influenza viruses A, B and C. Influenza-A viruses are further subdivided (subtyped) on the basis of the surface hemagglutinin (H) and neuraminidase (N) antigens. H1N1 is a type of influenza-A virus.
- In addition to humans, influenza also infects a variety of animal species. More than 100 types of influenza A infect most species of birds, pigs, horses, dogs, and seals. Influenza B has also been reported in seals. In this context, the term avian influenza (or "bird flu") refers to zoonotic human infection with an influenza strain that primarily affects birds. Swine influenza refers to infections from strains derived from pigs.
- Type A is responsible for major epidemics and B for localized outbreaks. Epidemics usually occur during the winter months. Influenza-A pandemics also occur and cause considerable school and work absenteeism. Influenza-B causes less severe outbreaks mostly in schools and military camps. Influenza-C rarely causes human disease.
- A remarkable feature of influenza virus A is that it can undergo periodic antigenic variations. Major antigenic variations, called antigenic shifts, are associated with pandemics and are seen with influenza-A viruses only. Minor variations are called antigenic drifts. Antigenic shift happens due to re-assortment of gene segments between viral strains and 'antigenic drift' from point mutations.

Pathogenesis

- The disease is acquired by inhalation of droplets generated by coughs and sneezes.
- It can also spread through hand-to-hand contact, personal contact, and fomites.
- The infection involves the ciliated columnar epithelial cells, but can also involve alveolar cells, mucous gland cells and macrophages. The infected cells of the tracheobronchial tree eventually become necrotic and desquamate.
- The host response to influenza involves both cell mediated and humoral immunity.
- Systemic symptoms in influenza, like fever may be related to the induction of cytokines.

Clinical Manifestations

- The incubation period varies from 18 to 72 hours.
- Initially respiratory symptoms like dry cough and rhinorrhoea are present but are later overshadowed by systemic symptoms.
- Systemic symptoms include fever, chills, headache, myalgia, arthralgia and loss of appetite. Rigors are rare. Fever may last for as long as a week.
- Systemic examination is usually normal.
- Most patients recover in 1 week, although cough may persist for 1 to 2 weeks longer. In some patients weakness may persist for several weeks.
- Complications include secondary bacterial pneumonia, Reye's syndrome, myocarditis, encephalitis, transverse myelitis and, rarely, Guillain-Barré syndrome.

Diagnosis

- Laboratory diagnosis is accomplished by the detection of virus or viral antigen in throat swabs, nasal washes, or sputum.
- *Rapid diagnostic tests*: These employ immunological and molecular techniques. Options include immunofluorescence (IF) assays, enzyme immunoassays (EIA), and polymerase chain reaction (PCR)-based testing.
- *Serology*: Diagnosis can be established retrospectively by serologic methods such as hemagglutination-inhibition.

Treatment

- Most cases of influenza resolve spontaneously without any complications. Symptomatic therapy with paracetamol for fever and myalgia, codeine syrup for dry cough are enough for such cases. Aspirin should be avoided because of the risk of Reye's syndrome. Patients should be advised to rest and maintain hydration during acute illness.
- *Antiviral drugs are available to treat influenza*: Amantadine and rimantadine for influenza A and the neuraminidase inhibitors zanamivir and oseltamivir for both influenza A and influenza B.
- Antibiotics are indicated for secondary bacterial infections.

Prevention

- An inactivated influenza vaccine active against both influenza A and B provides 80% protective efficacy. It is given intramuscularly.
- Recently, a live attenuated influenza vaccine which can be administered as intranasal spray is available. This vaccine is also effective against both influenza A and B and has 92% protective efficacy. It can be used in healthy children and adults from 5 to 49 years of age.
- Vaccination should be offered to chronically ill patients and persons over the age of 65 years.

Q. Discuss the etiology, clinical features, diagnosis and management of H1N1 influenza (swine flu).

- Swine influenza is a highly contagious respiratory disease in pigs caused by one of several swine influenza A viruses. In addition, influenza C viruses may also cause illness in swine. The current virus is a novel influenza A (H1N1) virus not previously identified in humans (H = hemagglutinin, N = neuraminidase). Outbreaks of H1N1 influenza (swine flu) are common in pigs year-round.
- Transmission of swine influenza viruses to humans is uncommon. However, transmission can occur to humans via contact with infected pigs or environments contaminated with swine influenza viruses. Once a human becomes infected, he or she can then spread the virus to other humans.
- The current H1N1 influenza (swine influenza) outbreak has been reported worldwide. In 2009, cases of influenza-like illness were first reported in Mexico on March 18; the outbreak was subsequently confirmed as H1N1 influenza A. Subsequently the US Department of Health and Human Services declared a national public health emergency involving H1N1 influenza A. During this outbreak, nearly 100,000 were hospitalized, and about 3900 died. On June 11, 2009, WHO raised the pandemic alert level to phase 6 (indicating a global pandemic) because of widespread infection beyond North America to Australia, the United Kingdom, Argentina, Chile, Spain, and Japan. World Health Organization (WHO) reported that H1N1 influenza had been confirmed in over

200,000 people in more than 100 countries. In October 2009, President Obama declared the 2009 H1N1 influenza pandemic a national emergency. Currently WHO and Centers for Disease Control and Prevention (CDC) are monitoring the situation all over the world.

Clinical Features

- Manifestations of H1N1 influenza (swine flu) are similar to those of seasonal influenza. Patients present with symptoms of acute respiratory illness, such as fever, chills, fatigue, cough, sore throat, body aches, and headache. In addition, diarrhea and vomiting may occur.
- Clinical deterioration is characterized by primary viral pneumonia, which destroys the lung tissue and does not respond to antibiotics, and multi-organ dysfunction including the heart, kidneys, and liver. Patients with severe disease have dyspnea, cyanosis, dehydration, and altered mental status.

Diagnosis

Clinicians should consider the possibility of H1N1 infection in patients who present with febrile respiratory illness. The CDC criteria for suspected H1N1 influenza are as follows:

- Onset of acute febrile respiratory illness within 7 days of close contact with a person who has a confirmed case of H1N1 influenza A virus infection, or
- Onset of acute febrile respiratory illness within 7 days of travel to a community (within the United States or internationally) where one or more H1N1 influenza A cases have been confirmed, or
- Acute febrile respiratory illness in a person who resides in a community where at least one H1N1 influenza case has been confirmed.

If H1N1 is suspected, the clinician should obtain a respiratory swab and send it for H1N1 testing.

Laboratory Confirmation of Diagnosis

- Real-time RT-PCR is the recommended test for confirmation of novel influenza A (H1N1) cases.

Management

Supportive Therapy

- Patients should be isolated to prevent spread of infection to others. Bedrest, increased fluid intake, cough suppressants, antipyretics and analgesics (e.g. acetaminophen, nonsteroidal anti-inflammatory drugs) for fever and myalgias. Severe cases may require intravenous hydration and ventilator support.

Antiviral Agents

- Serious patients should be treated with antiviral agents. Drugs of choice are oseltamivir (TAMIFLU) or zanamivir. These two drugs inhibit neuraminidase on the surface of influenza virus that destroys an infected cell's receptor for viral hemagglutinin. By inhibiting viral neuraminidase, these agents decrease the release of viruses from infected cells and, thus, viral spread.
- Antiviral drugs reduce the risk of pneumonia, a leading cause of death in H1N1 and the need for hospitalization. Oseltamivir should be started as early as possible (preferably within 48 hours) in a dose of 75 mg bd for 5 days. Where oseltamivir is unavailable or cannot be used for any reason, zanamivir may be given. Zanamivir is given by inhalation in a dose of 10 mg bd for 5 days. Pregnant women and patients with underlying medical conditions are at higher risk of developing complications and should be given antivirals as soon as H1N1 is suspected even before laboratory confirmation.

Reducing the Spread of Infection

- Patients who develop flu-like illness (i.e. fever with either cough or sore throat) should be strongly encouraged to self-isolate in their home for 7 days after the onset of illness or at least 24 hours after symptoms have resolved, whichever is longer.
- While in home isolation, patients and other household members should be given infection control instructions, including frequent handwashing with soap and water. Use alcohol-based hand gels (containing at least 60% alcohol) when soap and water are not available and hands are not visibly dirty. Patients with H1N1 influenza should wear a face mask when within 6 feet of others at home.
- If the patient must go into the community (e.g. to seek medical care), he or she should wear a face mask.
- Patients should call the physician before meeting and should avoid mixing with other OPD patients at clinic or hospital.
- Prophylaxis with antiviral agents should be considered for close household contacts of a confirmed or suspected case who are at high risk for complications (e.g. chronic medical conditions, persons >65 y or <5 y, pregnant women), schoolchildren at high risk for complications who have been in close contact with a confirmed or suspected case, healthcare providers who were not using appropriate personal protective equipment during close contact with a confirmed or suspected case. Antivirals should not be used for postexposure chemoprophylaxis in healthy children or adults.
- School closure should be considered upon a confirmed case of H1N1.

- Public gatherings should be avoided in a place where there has been a confirmed case of H1N1.

Vaccine

- Vaccine stimulates active immunity to influenza virus infection by inducing production of specific antibodies. H1N1 vaccine is available as an IM injection and as an intranasal product.
- Intramuscular vaccine contains monovalent, inactivated influenza-A virus. It is given as 0.5 ml IM in deltoid muscle. Two doses are required for children younger than 10 years (initial dose followed by a booster several weeks later). Single dose is recommended for adults and children 10 years and older. Intranasal vaccine is given as 0.2 ml/dose (0.1 ml per nostril) intranasally (1 dose).
- Vaccination is recommended for pregnant women, household contacts and caregivers of children younger than 6 months, healthcare and emergency medical services personnel, children aged 6 months to 18 years, young adults aged 19–24 years, and persons aged 25 through 64 years with underlying medical conditions such as heart disease, COPD, diabetes, etc.

Prognosis

- H1N1 influenza tends to cause high morbidity but low mortality rates (1–4%). Complications are more likely in children, elderly, pregnant women and people with other co-morbid illness.

Q. Varicella (chickenpox) (HHV-3).

Q. Herpes zoster (shingles).

- Varicella-zoster virus (VZV; human herpes virus-3) is a DNA virus and belongs to herpesviridae family.
- *It produces two clinical entities*: Varicella (chickenpox) and herpes zoster (shingles).
- Chickenpox is the primary infection, and usually occurs in childhood. Chickenpox rarely occurs twice but the virus remains latent in the dorsal root and cranial nerve ganglia. Years later it may be reactivated to cause vesicular eruption in the relevant sensory dermatomes which is known as herpes zoster (shingles). Sometimes the virus may affect a motor nerve such as the facial nerve to produce facial palsy.

Varicella (Chickenpox)

- Chickenpox affects children commonly.
- Incubation period is 10 to 21 days.
- There may be a prodrome of low grade fever, headache and malaise lasting 1–2 days before the onset of rash.
- Rashes appear first on the face and trunk and then spread to other parts of the body. Lesions can also be found on the mucosa of the pharynx and vagina. Rashes may be pruritic and centripetal with relative sparing of the peripheries. To start with rashes are maculopapular and in a few hours become vesicles. Vesicles become pustules which later form crusts. New lesions continue to appear for 2–4 days so that all stages of the eruption are present simultaneously (pleomorphic rash). Rashes usually heal without scarring. Lesions can get secondarily infected with bacteria, usually *Streptococcus pyogenes* or *Staphylococcus aureus.*
- Complications include CNS involvement in the form of cerebellar ataxia, meningitis, encephalitis, transverse myelitis, Guillain-Barré syndrome, varicella pneumonia, myocarditis, nephritis, hepatitis and arthritis. Reye's syndrome (hepatic encephalopathy), another complication, is associated with aspirin therapy.
- The clinical diagnosis can be confirmed where necessary by isolation of virus in tissue culture, demonstrations of high titres of antibodies or the detection of VZV DNA by PCR. Tzanck smear made by scraping of the base of the lesions may show multinucleated giant cells.
- Most people recover with supportive treatment. Antibiotics may be used for secondary skin infection. Antiviral agents like acyclovir, famciclovir and valacyclovir are recommended for adolescents and adults with chickenpox of ≤24 hours duration.

Herpes Zoster (Shingles)

- Herpes zoster is the consequence of reactivation of latent VZV from the dorsal root ganglia.
- The first symptom is severe burning or shooting pain in the affected dermatome followed by erythematous maculopapular eruption in 2 to 3 days. These eruptions turn into vesicles and start crusting. The skin eruption is unilateral.
- The total duration of disease is generally between 7 and 10 days.
- Local skin hyperalgesia is a clue to the neural origin.
- The dermatomes from T3 to L3 are commonly affected.
- In ophthalmic herpes the Gasserian ganglion is affected and the ophthalmic branch of the trigeminal nerve is involved. Lesions develop on the nose, conjunctiva and cornea of the affected side. Corneal lesions heal leaving behind opacities causing blindness.
- Complications of herpes zoster are postherpetic neuralgia and CNS involvement. In postherpetic neuralgia pain persists even after the lesions have healed. CNS complications include meningoencephalitis and transverse myelitis. Sometimes weakness and wasting

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in segments supplied by the nerve root may occur due to motor neuritis. Immunocompromised patients can develop severe disease with multi-organ involvement.

- *Treatment*: Antiviral drugs are indicated for the treatment of shingles. Drugs used are same as for varicella (acyclovir, famciclovir and valacyclovir). Herpes zoster causes severe pain which may be difficult to control. NSAIDs, opioid analgesics can be used along with neuron modulator drugs such as carbamazepine, gabapentin, amitriptyline and lidocaine patches to control pain.

Q. Infectious mononucleosis (glandular fever).

Etiology

- Infectious mononucleosis (IM) is a disease caused by Epstein-Barr virus (EBV). EBV is a DNA virus belonging to the family Herpesviridae. EBV also causes many tumors in human beings like nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and B cell lymphoma.
- Infectious mononucleosis (IM) is also known as *glandular fever* or *kissing disease*. Later it was called infectious mononucleosis because it is characterized by absolute lymphocytosis and atypical mononuclear cells in the blood.
- It is characterized by a triad of fever, tonsillar pharyngitis, and lymphadenopathy.

Pathogenesis

- In humans it spreads commonly through saliva ('the kissing disease') and rarely by blood transfusion.
- After entry into the body the virus multiplies primarily in B-lymphocytes but also may replicate in the epithelial cells of the pharynx and parotid duct. Infected B cells are responsible for the dissemination of infection throughout the lymphoreticular system, i.e. liver, spleen, and peripheral lymph nodes. Infected B lymphocytes produce antibodies against the virus. Cytotoxic T cells are also produced by the body against the EBV-infected B lymphocytes.

Clinical Features

- Incubation period is 4–8 weeks. Infectious mononucleosis is a disease of childhood, adolescence and low socio-economic groups.
- Initially there is a prodrome of fatigue, malaise, and myalgia.
- Prodrome is followed by typical features such as fever, sore throat, and lymphadenopathy.
- Fever is usually low grade. Lymphadenopathy most often affects the posterior cervical nodes but may be generalized. Rarely hepatosplenomegaly may be found.
- A generalized maculopapular, urticarial, or petechial rash is occasionally seen. Rash may develop if ampicillin is taken.
- IM should be suspected in an adolescent or young adult with fever, sore throat and lymphadenopathy (especially posterior cervical lymphadenopathy).
- The illness usually lasts 2–4 weeks but weakness can persist for a long time.
- Complications include splenic rupture, thrombocytopenia, autoimmune hemolytic anemia, meningitis, encephalitis, and GB-syndrome.

Investigations

- Blood tests show raised leucocyte count with atypical lymphocytosis.
- Liver enzymes may be raised but jaundice is rare.
- Paul-Bunnel test and Monospot test (detect heterophile antibodies) are usually positive.
- Demonstration of antibodies to viral capsid antigen (i.e. VCA-IgG and VCA-IgM).

Differential Diagnosis

- *Other infections which produce fever and lymphadenopathy*: Streptococcal pharyngitis, cytomegalovirus, acute HIV, or toxoplasma.
- Lymphoma.

Treatment

- There is no specific treatment for infectious mononucleosis. Antiviral drugs do not have much benefit.
- Supportive measures, rest and antipyretics are given as required.
- Ampicillin should be avoided in suspected infectious mononucleosis because it causes rash.
- Steroids have a role in severe thrombocytopenia, autoimmune hemolytic anemia and tonsillar enlargement causing airway obstruction.

Q. Chronic fatigue syndrome.

- Chronic fatigue syndrome (CFS) is a disorder characterized by unexplained, persistent, and sometimes debilitating fatigue.
- It can be difficult to diagnose because there are no objective clinical or laboratory findings associated with this disorder.

Etiology

- The etiology of CFS is unclear and is likely complex.
- These complex factors, along with the numerous psychiatric comorbidities of CFS, have led some experts to question whether any organic etiology exists.
- Current research on CFS focuses on the abnormalities of immune and adrenal systems, genetics, the biopsychosocial model, and sleep and nutrition.

Clinical Features

- CFS is more common in young and middle-aged adults, in women and in caucasians.
- Persistent fatigue is the hallmark of CFS. Fatigue often follows an infection such as upper respiratory infection or mononucleosis. Patient is left with overwhelming fatigue even after he recovers from the initial illness. Physical activity worsens fatigue. Many patients with CFS also have other symptoms such as feeling feverish, muscle and joint aches, intermittent tenderness or swelling in the lymph nodes.
- Many patients have underlying depression.

Diagnostic Criteria for Chronic Fatigue Syndrome

- Severe fatigue for longer than six months, and at least four of the following symptoms:
  - Headache of new type, pattern, or severity
  - Multijoint pain without swelling or erythema
  - Muscle pain
  - Postexertional malaise for longer than 24 hours
  - Significant impairment in short-term memory or concentration
  - Sore throat
  - Tender lymph nodes
  - Unrefreshing sleep.

Treatment

- There is no specific therapy.
- Cognitive behavioral therapy and graded exercise programs have been shown to be beneficial.
- Low dose of a tricyclic antidepressant may help most patients.
- Treatment of co-morbid illness such as depression, sleep disturbances, etc.

Q. Human papillomavirus infections.

- Human papillomaviruses are DNA viruses belonging to the family papillomaviridae.
- They infect the skin and mucous membranes. Infections produce warts or may be associated with a variety of benign and malignant neoplasms. Some HPV infections (such as 16, 18, 31, 33, and 45) cause cervical cancer.
- Most of the infections are seen in children and young adults. Warts can be common warts (verruca vulgaris), plantar warts (verruca plantaris) or anogenital warts (condyloma acuminatum). Anogenital warts are sexually transmitted.
- Complications of warts include itching and bleeding with secondary infection. Warts in the respiratory tract may obstruct the airway.
- Many HPV lesions resolve spontaneously. Treatment options are cryosurgery, application of caustic agents, electrodesiccation, surgical excision, and ablation with a laser. Topical antimetabolite, such as 5-fluorouracil is also effective.

Q. Measles (rubeola).

- Measles (also known as rubeola) is a highly contagious, acute, viral exanthematous disease.

Etiology

- Measles is caused by measles virus which is a RNA virus belonging to the family of paramyxoviruses.

Epidemiology

- It most commonly affects preschool children. Incidence of measles has come down after the introduction of measles vaccine.
- Measles virus is transmitted by inhalation of respiratory droplets. It can also spread through direct contact with larger droplets.
- The virus is present in nasopharyngeal secretions, blood and urine during the prodromal period and for a short time after the rash appears.
- Patients are contagious from 1 or 2 days before the onset of symptoms until 4 days after the appearance of the rash. Infectivity is maximum during the prodromal phase.

Clinical Features

- Incubation period is 10 to 14 days.
- Measles starts with a prodrome of malaise, cough, lacrimation, nasal discharge, and fever. At this stage it resembles influenza.
- Just before the onset of the rash, Koplik's spots appear as 1–2 mm blue-white spots on a bright red background. Koplik's spots are usually seen on the buccal mucosa alongside the second molars. They are characteristic of measles because they are not seen in any other disease. The spots disappear after the onset of rash.
- Rash appears 3–4 days after the onset of fever. Rash begins first at the hairline and behind the ears, and then spreads to the trunk and limbs. Rashes do not spare the

palms and soles, are erythematous, nonpruritic, and maculopapular. Rash is monomorphic, i.e. all rashes have similar morphology. Rash begins to fade by the fourth day, in the order in which it appeared.

- The entire illness lasts about 10 days. The disease tends to be more severe in adults than in children.

Diagnosis

- In clinical practice, measles is diagnosed mainly by clinical features.
- Laboratory diagnosis is most frequently made serologically using serum anti-measles IgM antibody. IgM antibody is detectable three days after the appearance of rash. Anti-measles IgG antibody appears 7 days after the appearance of rash.
- A quick diagnosis of measles can be made by demonstration of measles antigen by immunofluorescent staining of a smear of respiratory secretions.
- Measles virus can be cultured and isolated from respiratory secretions or urine.
- PCR for measles virus RNA can also diagnose measles.

Treatment

- There is no specific treatment for measles.
- Patient should be isolated.
- Most people recover spontaneously and only supportive treatment is necessary.
- Ribavirin may be considered for use in immunocompromised individuals.
- Administration of vitamin-A has been shown to prevent complications especially in malnourished children.
- Secondary bacterial complications are treated with appropriate antibiotics.

Complications

- ***Respiratory tract complications***: Laryngitis, croup, or bronchitis, otitis media, pneumonia.
- ***CNS complications***: Encephalitis, transverse myelitis, subacute sclerosing panencephalitis (SSPE). SSPE is a chronic, rare form of measles encephalitis. It is common in children who have measles before the age of 2 years. SSPE is now rare due to widespread vaccination against measles. Clinical features are progressive dementia which evolves over several months.
- ***Gastrointestinal complications***: Hepatitis, appendicitis, and mesenteric adenitis
- ***Others***: Myocarditis, glomerulonephritis, postinfectious thrombocytopenic purpura and reactivation of tuberculosis.

Prevention

- Immediate protection can be obtained by giving immunoglobulin within 6 days of exposure to the disease. Measles vaccine given within 72 hours of exposure may also protect against disease.
- Active immunization with measles vaccine is included in the national immunisation programme. A single dose of vaccine is given at 8 to 9 months of age. It provides lifelong immunity. Giving MMR vaccine at 15 to 18 months takes care of occasional failure of measles vaccine given at 8 to 9 months of age. However, if there is an epidemic of measles, vaccination may be given at 6 months of age followed by another dose or MMR vaccine at 15 months.

Q. Mumps.

- Mumps is an acute, communicable, systemic viral infection whose most distinctive feature is swelling of parotid glands. It can involve other salivary glands, meninges, pancreas, and the gonads.

Etiology

- Mumps is caused by mumps virus which is a member of the paramyxovirus group. It is a RNA virus.

Epidemiology

- Mumps occurs worldwide but the incidence has decreased after the introduction of mumps vaccine (MMR).
- Mumps occurs mainly during winter and spring. It is mainly a disease of childhood, but nowadays adults are getting affected more commonly. Both sexes are affected equally.
- Epidemics occur in close populations, such as in schools and military services.
- Mumps is highly infectious and spreads rapidly among susceptible people living in close quarters.
- Mumps virus is transmitted by droplet nuclei, saliva, and fomites. Fomites contaminated by infected saliva and possibly also by urine transmit the infection. Transmission of infection occurs a day before the appearance of the parotid swelling and for about three days after the swelling disappears.
- One attack of mumps or vaccination confers lifelong immunity.

Clinical Features

- Incubation period is 2–3 weeks.
- Mumps starts with a prodrome of fever, malaise, myalgia, and anorexia.

- Parotitis may develop within the next 24 h or may be delayed up to a week. Parotitis is usually bilateral, although sometimes only one side is affected. Parotid glands are involved most commonly and submaxillary and sublingual glands are involved rarely. Parotid gland becomes swollen and tender. Gland swelling increases for a few days and then gradually subsides within a week.
- Other than parotitis, orchitis is the most common manifestation. Testis becomes swollen, painful and tender. Testicular atrophy develops in half of the affected men. However, since orchitis is usually unilateral and other testes remains unaffected, sterility is rare. Oophoritis can occur in women but less common than orchitis and does not lead to sterility.
- Aseptic meningitis is a common manifestation of mumps in both children and adults. Mumps meningitis is usually self-limiting, although cranial nerve palsies are rarely seen. Rarely, encephalitis can occur, which presents as high fever with altered sensorium. Other CNS problems occasionally seen are cerebellar ataxia, facial palsy, transverse myelitis, Guillain-Barré syndrome, and aqueductal stenosis leading to hydrocephalus.
- Other clinical manifestations are pancreatitis, myocarditis, mastitis, thyroiditis, nephritis, arthritis, and thrombocytopenic purpura.

Differential diagnosis

- Mumps has to be differentiated from other causes of parotid gland swelling, such as:
  - Influenza, parainfluenza and coxsackie virus infections
  - Bacterial parotitis due to staphylococcal infection
  - Obstruction of Stenson's duct by a calculus
  - Parotid tumor
  - Sarcoidosis
  - Sjogren's syndrome

Diagnosis

- Diagnosis is mainly by clinical features.
- Serological detection of IgM antibodies.
- Virus isolation by culturing appropriate clinical specimens.
- PCR.

Treatment

- Symptomatic treatment; analgesics and antipyretics for fever and pain, cold compresses for parotid swelling.
- Patients with meningitis or pancreatitis may require hospitalization for intravenous fluids.
- Patients with orchitis are also treated symptomatically with bed rest, nonsteroidal antiinflammatory agents, support of the inflamed testis and ice packs.

Prevention

- Patients should be isolated to prevent transmission to others.
- Passive immunisation using immunoglobulin is not effective to prevent infection in close contacts and is not recommended.
- Active immunisation is routinely given as MMR vaccine (measles, mumps, rubella) subcutaneously at 15 months of age or later; repeat dose may be necessary after 5–10 years. MMR vaccine is also recommended for susceptible older children, adolescents, and adults, particularly adolescent males who have not had mumps. Vaccine should not be given to pregnant women, immunosuppressed patients, or persons with advanced malignancies.

Q. Rubella (German measles).

- Rubella is an acute viral exanthematous disease caused by rubella virus, a RNA virus.
- It is also known as German measles because it was first recognized to be different from measles in Germany.

Epidemiology

- Humans are the only natural hosts for rubella infection.
- It spreads by respiratory droplets or is maternally transmitted to the fetus causing congenital infection.
- The peak incidence of the disease is in children of 5–12 years of age.

Clinical Manifestations

- The incubation period is usually 2–3 weeks.
- The disease is characterized by fever, rash, and lymphadenopathy.
- It is more severe in adults than children.
- There is usually a prodrome of low grade fever, malaise, anorexia and sore throat, followed by lymphadenopathy and appearance of skin rash. Rash often begins on the face and spreads down the body. It is maculopapular but not confluent. It disappears in the same order. Lymphadenopathy usually affects suboccipital, cervical and post-auricular nodes but rarely axillary nodes can also be involved. Complications are rare and include arthritis (in women), encephalitis and thrombocytopenia.
- *Congenital rubella*: Maternal infection in early pregnancy can lead to fetal infection, leading to teratogenic effects and congenital rubella. Sensorineural hearing loss is the most common manifestation of congenital rubella syndrome. Other signs of congenital rubella are cataract, heart disease (patent ductus arteriosus), deafness, and many other defects like mental

retardation, microcephaly, and thrombocytopenic purpura. Infection in the first trimester leads to more severe congenital rubella in the fetus.

Investigations

- Most cases are mild and are difficult to diagnose on clinical grounds.
- Rubella can be diagnosed by specific IgM rubella antibody and also by virus isolation.

Treatment

- Isolate the patient for 7 days after the onset of rash to prevent infection to others.
- There is no specific treatment. Most cases recover spontaneously.
- Antipyretics like paracetamol can be used to treat fever.

Prevention

- Presently all infants are routinely immunized against rubella by giving MMR vaccine at 12–15 months of age. Live rubella virus vaccine containing RA 27/3 strain, and a recombinant DNA vaccine is now available.
- Vaccine is administered in a single dose of 0.5 ml subcutaneously. Immunity wanes after 10–15 years and hence the vaccine may have to be repeated at 10–15 years of age. Rubella vaccine may also be administered to anyone who is thought to be susceptible to the infection.
- Live rubella vaccine is contraindicated during pregnancy and it is recommended that pregnancy be avoided for at least 3 months after rubella vaccination.

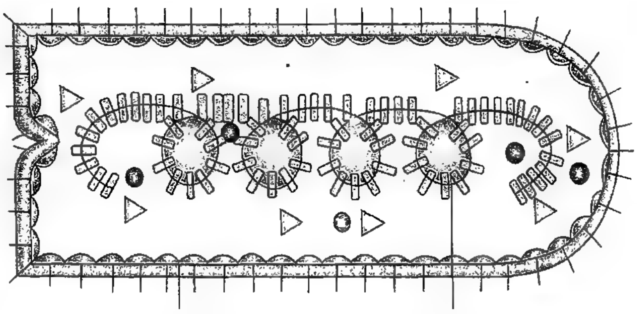

Fig. 1.9: Rabies virus

Q. Discuss the etiology, epidemiology, pathogenesis, clinical features, diagnosis and treatment of rabies.

Q. Prevention of rabies.

Q. Postexposure prophylaxis of rabies.

- Rabies is an acute lethal viral infection of the central nervous system caused by rabies virus. It is a preventable zoonotic disease.
- Rabies is one of the oldest, best known, and most feared human diseases. It has the highest case fatality rate of any infectious disease.

Etiology

- Rabies virus is a bullet shaped virus, with a single-stranded ribonucleic acid (RNA) nucleocapsid core and lipoprotein envelope. It belongs to the family of Rhabdoviridae and genus Lyssavirus.

Epidemiology

- Rabies has a worldwide distribution except Antarctica, New Zealand, and Japan.
- Mammals are the main reservoir of rabies virus.
- Rabies exists in two forms: (1) urban rabies, found in unimmunized domestic dogs and cats, and (2) sylvatic rabies, found in skunks, foxes, raccoons, mongooses, wolves, and bats.
- The main reservoir of rabies throughout the world is the domestic dog. Domestic animals usually acquire infection from sylvatic reservoirs of infection.
- Human infection occurs through contact with un-immunized domestic animals or from exposure to wild animals.
- Mandatory vaccination of domestic dogs against rabies has resulted in decreased incidence of rabies.

Pathogenesis

- Rabies is a highly neurotropic virus that evades immune surveillance by its sequestration in the nervous system.
- Rabies is transmitted by the bite of infected animals, commonly dogs or cats. The saliva of these animals is the reservoir of infection. Rarely, transmission takes place through transplantation of infected tissues such as cornea or inhalation of aerosol containing virus.
- After the entry of live virus through saliva following a bite, viral replication starts in striated muscle cells. The virus then spreads centripetally up the nerve to the CNS, via peripheral nerve axoplasm, at a rate of ~3 mm/h. Once the virus reaches the CNS, it multiplies there and then passes centrifugally along somatic and autonomic nerves to other tissues—the salivary glands, adrenal medulla, kidneys, lungs, liver, skeletal muscles, skin, and heart. In the salivary glands virus can multiply again inside acinar cells and secreted into saliva which is infective to others.
- The most characteristic pathologic finding of rabies in the CNS is the formation of cytoplasmic inclusions called

Negri bodies within neurons. Negri body is an eosinophilic mass of fibrillar matrix and viral particles. Anatomically, Negri bodies are located in Ammon's horn, the brainstem, hypothalamus, amygdaloid nucleus, cerebral cortex and dorsal root ganglion. Negri bodies are not found in at least 20% cases of rabies, hence, their absence does not rule out the diagnosis of rabies.

Clinical Features

Incubation Period

- The incubation period of rabies ranges from 10 days to over 1 year (mean 1–2 months). Rarely, cases of human rabies with an extended incubation period (2 to 7 years) have been reported. The incubation period depends on the amount of virus introduced, host defense mechanisms, and the distance that the virus has to travel from the site of inoculation to the CNS.
- Incubation period is less than 50 days if the patient is bitten on the head or neck or if a heavy amount of virus is inoculated. A person with a scratch on the hand may take longer to develop symptoms of rabies than a person who receives a bite to the head.
- The rabies virus is segregated from the immune system during this period, and no antibody response is observed.

Prodromal Period

- *Prodromal stage*: This stage lasts 1–4 days and is characterised by fever, nausea, vomiting, headache, myalgia, sore throat and dry cough. There may be complaint of paresthesia, fasciculations or intense itching at the site of virus inoculation which is pathognomonic of rabies and occurs in 50% of cases during this phase. These sensations are due to the multiplication of virus in the dorsal root ganglion of the sensory nerve supplying the area. Except for these sensations/fasciculations all other symptoms resemble any other viral prodrome.

Acute Neurologic Period

- Two acute neurologic forms of rabies are seen in humans: Encephalitic (furious) in 80% and paralytic (dumb) in 20%.
- Encephalitic rabies presents with hydrophobia, aerophobia, pharyngeal spasms, and hyperactivity. This is the most common form. This stage is characterized by periods of excessive motor activity, excitation, agitation, hallucinations, confusion, muscle spasms, meningismus, opisthotonic posturing, seizures, and focal paralysis. Initially they are interspersed with lucid intervals, but as the disease progresses the lucid periods get shorter until the patient lapses into coma. Hyperaesthesia, with excessive irritation to bright light, noise, touch, and breezes are often seen. Abnormalities of the autonomic nervous system include dilated pupils, increased sweating, lacrimation, salivation and postural hypotension. There may be fever at this stage. Evidence of upper motor neuron paralysis, with weakness, exaggerated deep tendon reflexes, and extensor plantar responses, is always found. Paralysis of the vocal cords may produce dysphonia. *Brainstem dysfunction* begins shortly after encephalitic phase. Brainstem dysfunction manifests as diplopia, facial paralysis, and dysphagia with excessive salivation. The combination of excessive salivation and difficulty in swallowing give the appearance of "foaming at the mouth." Attempt to swallow liquids produces painful, violent, involuntary contraction of the diaphragmatic, accessory respiratory, pharyngeal, and laryngeal muscles called *hydrophobia*. Hydrophobia is seen in only ~50% of rabies cases. Even blowing air can produce violent spasms (*aerophobia*).
- Paralytic (dumb) rabies presents as quadriparesis with sphincter involvement, mimicking Guillain-Barré syndrome. Encephalitis occurs late in the course.

Stage of Coma and Death

- This begins within 10 days of onset, and the duration varies. The patient soon lapses into coma, and dies of respiratory failure. After the onset of brainstem symptoms, patient survives for only 4–5 days and rarely for 20 days maximum. If artificial supportive measures are instituted, patient may survive longer but many complications may appear like hypotension, cardiac arrhythmias, ARDS, etc. which can kill the patient.

Diagnosis

- Diagnosis is usually made based on clinical features and history of exposure to rabies source (dog bite).
- Routine blood tests are nonspecific.
- ***Demonstration of virus*** in patient's CSF, serum, saliva, and full-thickness skin biopsy sample from the nape of the neck.
- ***Demonstration of antibodies against rabies virus***: Rabies virus-specific antibodies may be found in serum as a result of previous vaccination against rabies. However, detection of antibodies in a previously unimmunized patient is diagnostic of rabies. Finding rabies virus antibodies in the CSF is diagnostic of rabies encephalitis.
- ***Rt–PCR amplification***: Detection of rabies virus RNA by Rt–PCR is highly sensitive and specific. This technique can detect virus in fresh saliva samples, CSF, and skin and brain tissues.
- ***Direct fluorescent antibody testing***: Direct fluorescent antibody (DFA) testing with rabies virus antibodies

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Epidemiology

- Amebiasis is found all over the world.
- Amebiasis is more common in the developing world, where overcrowding, poor sanitation and economic backwardness are common. In developed countries, it is an important infection among male homosexuals, intravenous drug users and patients with AIDS.
- 90% of infections are asymptomatic and only 10% produce clinical symptoms.

Life Cycle of Ameba and Pathogenesis

- The infection is transmitted through the faeco-oral route.
- Man is the only reservoir of infection and excretes the cystic form of the organism in the feces, which can survive in the environment for several weeks. Man acquires infection by ingestion of viable cysts from fecally contaminated water, food, or hands. Less commonly it is acquired through oral and anal sexual practices. Once ingested, cysts are able to resist the acidic gastric juice, and reach small intestine, where the cysts develop into motile trophozoites. Trophozoites remain as harmless commensals in the colon in most patients. However in some patients, the trophozoites invade the bowel mucosa, and cause colitis which presents clinically as dysentery.
- There are usually mucosal ulcers which typically have the shape of a flask in cross-section (wide base and narrow neck). Amebic ulcers occur most commonly in the rectum but may occur anywhere in the colon.
- Trophozoites can also enter the bloodstream and get carried to different organs like liver, lungs, or brain where they may produce abscesses. The necrotic contents of a liver abscess appear like "anchovy paste". Some trophozoites undergo encystation and produce infectious cysts which are shed in the stool and the life cycle can get repeated again.
- Trophozoites cannot cause infection because they are rapidly killed by exposure to air or stomach acid.

Clinical Features

- Amebic infections are clinically classified as intestinal and extraintestinal.

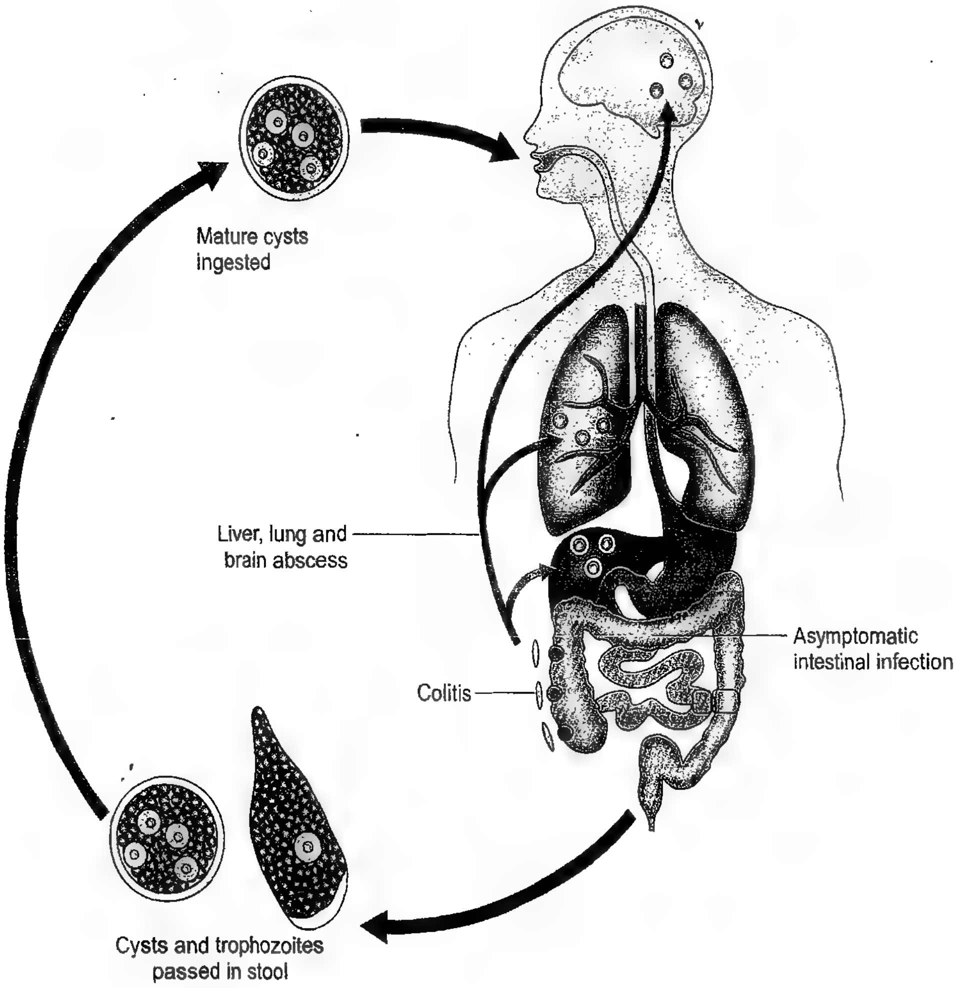

Fig. 1.12: Life cycle of ameba

Intestinal Amebiasis

- Most patients with intestinal amebiasis are asymptomatic. Those who become symptomatic present with dysentery. Lower abdominal pain, malaise and mild diarrhea develop gradually. Abdominal pain is usually colicky. Patients may pass up to 10 to 12 stools per day. The stools appear dark brown, contain a little fecal material and consist mainly of blood and mucus. Fever is uncommon unlike bacterial diarrhea. Almost all patients have blood in the stools.
- Severe intestinal infection may present with severe abdominal pain and high fever. Some patients may develop toxic megacolon where there is severe gaseous dilation of colon. Rarely patients develop chronic amebic colitis, which can be confused with inflammatory bowel disease.

Extraintestinal Amebiasis

- Extraintestinal infection by *E. histolytica* most often involves the liver. Other sites include the brain, spleen, lungs and pelvic organs.
- Patients present with fever and right-upper-quadrant pain. Pain is dull or pleuritic in nature and may radiate to the right shoulder. Point tenderness over the liver and right-sided pleural effusion is common. Hepatomegaly is usually seen, but jaundice is rare. Although the initial site of infection is the colon, most patients do not give a history of dysentery. Most abscesses occur in the right lobe of liver. Amebic liver abcess can present as PUO and should be considered in the differential diagnosis of fever of unknown origin.

Complications

- Perforation of amebic ulcers and toxic megacolon.
- Liver abscesses may become big and rupture into adjacent structures such as the pleural cavities, lungs, pericardium and peritoneum which can be fatal.

Investigations

- ***Stool examination*:** This is the best test to diagnose amebic dysentery. A saline preparation of freshly passed stool is examined for motile trophozoites. Cysts also may be seen. Stool can be cultured for *Entamoeba histolytica* and other bacteria.
- ***Colonoscopy or sigmoidoscopy*:** These are useful to see the typical ulcers and also to distinguish it from other ulcerative and inflammatory lesions like acute bacillary dysentery and ulcerative colitis, and to obtain swabs and biopsies for appropriate examinations.
- ***Ultrasonography*:** Useful to identify amebic liver abscess. It gives an assessment of the size and location of the abscess.
- ***Serological tests*:** Demonstration of presence of anti-amebic antibodies in the serum is an important way of diagnosing amebic infections. Enzyme-linked immunosorbent assays (ELISAs) and indirect hemagglutination test are used for this purpose.

Treatment

- Metronidazole 400 mg thrice a day for 7 days is effective.
- Newer agents like tinidazole, secnidazole or ornidazole are equally effective and allow less frequent dosing.
- Along with above agents, it is useful to give luminal amoebicides like diloxanide furoate or iodoquinol or Paromomycin which act in the gut lumen and have minimal systemic absorption. Asymptomatic cyst passers do not require treatment.
- Liver abscess requires the above drugs at a higher dosage. If liver abscess does not respond to medical therapy, it can be aspirated under ultrasound guidance by introducing a pig-tailed catheter. Chloroquine has also been used for patients with hepatic amebiasis.
- Complications such as perforation, toxic megacolon and stricture require appropriate surgical treatment.

Q. Describe the etiology, clinical features, diagnosis and treatment of giardiasis.

- Giardiasis is one of the most common parasitic diseases worldwide and is due to *Giardia lamblia* which is a protozoan. It causes intestinal disease and diarrhea.
- *Giardia lamblia* is a flagellated protozoan and has a pair of nuclei which give it an owl-eyed appearance. Flagellate are responsible for its motility.

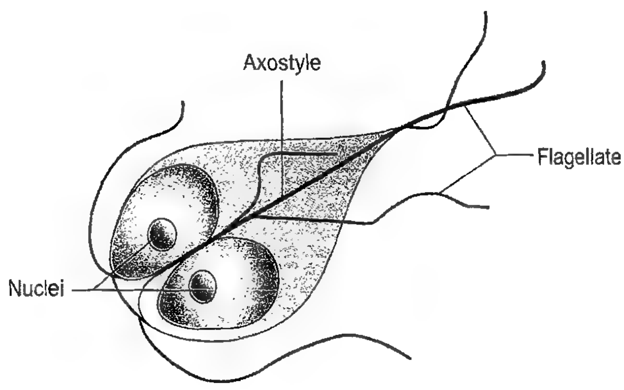

Fig. 1.13: *Giardia lamblia*

Pathogenesis

- Infection spreads through fecooral route and is acquired by ingestion of cysts present in food or water. The cysts excyst in the intestine and become trophozoites which have owl-eyed appearance. Giardia colonises the mucosa of upper small intestine but does not invade the mucosa.

- Giardia attach to the mucosa of duodenum and jejunum with the help of their ventral suction disc. They interfere with gut function by mechanical covering of the mucosa by a large number of parasites and causing villous atrophy in the jejunal mucosa leading to a reduced absorptive surface. In most infections the gut morphology is normal, but in a few cases there may be changes resembling tropical sprue and gluten-sensitive enteropathy on histopathology. The pathogenesis of diarrhea in giardiasis is not known.
- Both trophozoites and cystic forms are excreted in the stool, but only cysts are infective to others. High levels of secretory IgA in breast milk are believed to protect suckling infants from infection. Giardiasis is an important cause of travelers' diarrhea and is also an important cause of diarrhea in immunosuppressed individuals.

Clinical Features

- *Giardia* infection may or may not lead to symptoms. Most infected persons are asymptomatic.
- Acute giardiasis may manifest as diarrhea, abdominal pain, bloating, belching, flatus, nausea, and vomiting. This illness is usually self-limitimg. Patients may also present with dyspeptic symptoms with nausea and anorexia.
- Chronic giardiasis may present with malabsorption, steatorrhoea and weight loss. Such patients usually have villous atrophy, with malabsorption of fat, carbohydrates, vitamin B_{12} and lactose intolerance. Children with chronic giardiasis may have growth impairment.
- Giardiasis can be life-threatening in patients with hypogammaglobulinemia.

Diagnosis

- Giardiasis is diagnosed by the detection of parasite antigen, cysts or trophozoites in the feces.
- Endoscopic sampling of duodenal fluid and biopsy of the mucosa may be required to detect the parasite.

Treatment

- Metronidazole is the drug of choice and is given either as 200 mg thrice daily for 7 days or as a single dose of 2.4 g. Tinidazole or secnidazole are alternatives. All infected symptomatic persons should be treated.

Q. *Trichomonas vaginalis.*

- *Trichomonas vaginalis* is a pear-shaped protozoan and causes infection of the vagina, urethra and prostate.
- It spreads through sexual contact.

Clinical Features

- In women, it causes vaginitis which presents as yellow and frothy vaginal discharge with burning and itching. They may also complain of dysuria, increased urinary frequency and dyspareunia.
- In men, trichomoniasis presents with urethritis and prostatitis, but may be asymptomatic.

Diagnosis

- The diagnosis is made by detection of motile trichomonads in wet smears prepared from vaginal, urethral or prostatic secretions. Direct immunofluorescent antibody staining is more sensitive test than microscopy.

Treatment

- Metronidazole is the drug of choice and is given as 200 mg thrice a day for 7 days or as a single 2 g dose. Tinidazole also can be used. Both partners should be treated to prevent reinfection.

Q. Describe the etiology, clinical features, diagnosis and treatment of leishmaniasis.

- The term leishmaniasis refers collectively to various clinical syndromes caused by intracellular protozoa of the genus Leishmania. It is a vector-borne (sandfly) zoonosis, with rodents and canids as reservoir hosts and humans as incidental hosts.
- The clinical spectrum of leishmaniasis ranges from self-healing cutaneous ulcers to fatal visceral disease. These syndromes fall into three broad categories: cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML) and visceral leishmaniasis (VL).

Etiology

- The organisms causing various forms of leishmaniasis in humans belong to the subgenus Leishmania. Visceral leishmaniasis is usually caused by *Leishmania donovani,* cutaneous leishmaniasis by *L. tropica, L. major, L. aethiopica* and *L. mexicana,* and mucosal leishmaniasis by *L. amazonensis.*

Epidemiology

- Leishmaniasis mainly occurs in tropical and temperate regions. India and neighboring Nepal, Bangladesh, Sudan, and Brazil are the four largest foci of visceral leishmaniasis.
- Cutaneous leishmaniasis occurs mainly in Afghanistan, Pakistan, Ethiopia, Kenya, and Uganda.

Lifecycle and Pathogenesis

- Leishmania parasites are transmitted to man by the bite of female sandflies (phlebotomus) and lutzomyia. Visceral leishmaniasis can also be transmitted by blood transfusions or needle sharing.
- Leishmania exists in the sandfly as a motile, spindle-shaped promastigote with an anterior flagellum. As the flies feed on hosts including man, they regurgitate the promastigote stage into the skin. Promastigotes are phagocytized by macrophages and inside the macrophages develop into the nonflagellated amastigote stage. This amastigote multiplies by binary fission and are released after rupture of macrophages. Released amastigotes are phagocytized by other macrophages and start multiplying there. Some amastigotes can be ingested by sandflies where they transform back into promastigotes and ready to infect other hosts.
- There is inflammatory response against Leishmania organisms with increased production of gamma interferon (IFN), tumor necrosis factor alpha (TNF), and other proinflammatory cytokines. In addition to these proinflammatory cytokines and chemokines, patients with active disease also have markedly elevated levels of IL-10 in serum as well as in lesional tissues. IL-10 inhibits the killing of amastigotes by inhibiting macrophages. This inflammation along with inhibition of killing of amastigotes causes nodules, necrosis, ulceration and destruction of tissues seen in leishmaniasis.

Clinical Features

Cutaneous Leishmaniasis (CL)

- A few days or weeks after the bite of a sandfly, a papule develops and grows into a nodule that ulcerates. The base of the ulcer, which is usually painless, consists of necrotic tissue and crusted serum. Satellite lesions and local lymphadenopathy may be present.
- In diffuse cutaneous leishmaniasis, multiple, widespread nonulcerating cutaneous papules, nodules and infiltration is seen.
- Post-kala-azar dermal leishmaniasis (PKDL): Develops months to years after the patient's recovery from visceral leishmaniasis. Cutaneous lesions include hypopigmented macules, erythematous papules, nodules and plaques.

Mucosal Leishmaniasis (ML)

- Lesions in or around the nose or mouth are the typical presentation of ML. Patients usually give history of self-healed CL preceding ML by 1–5 years. Typically, ML presents as nasal stuffiness and bleeding followed by destruction of nasal cartilage, perforation of the nasal septum, and collapse of the nasal bridge. Subsequent involvement of the pharynx and larynx leads to difficulty in swallowing and phonation. The lips, cheeks, and soft palate may also be affected. Secondary bacterial infection is common, and aspiration pneumonia may be fatal.

Visceral Leishmaniasis (Kala-azar)

- Potentially lethal widespread systemic disease characterized by darkening of the skin as well as the pentad of fever, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia.

Diagnosis

- The diagnosis is established by demonstration of parasites. Amastigotes can be demonstrated by light-microscopic examination of a specimen (smear, biopsy) obtained from the infected site.
- Culture can be done in Novy-MacNeal-Nicolle (NNN) blood agar.
- Immunologic methods for diagnosis include serologic assays and skin testing for delayed-type hypersensitivity reactions. Traditional serologic methods like indirect fluorescent testing do not reliably distinguish past from current infection.
- Other methods of parasitologic confirmation include animal inoculation, and polymerase chain reaction (PCR).

Treatment

- Three groups of drugs are commonly used in the treatment of leishmaniasis
  - *Pentavalent antimonials*—sodium stibogluconate and meglumine antimoniate
  - *Pentamidine* isetheonate and pentamidine methanosulphonate
  - *Amphotericin B*
- All these antibiotics have to be given parenterally (IM or IV) for effective cure.
- *Miltefosine*: This is the first oral compound approved for the treatment of leishmaniasis. It has a long half-life (150–200 h) and its mechanism of action is not clearly understood.
- Allopurinol has also been used to treat leishmaniasis.

Q. Visceral leishmaniasis (kala-azar).

Etiology

- Visceral leishmaniasis (kala-azar) is caused by *Leishmania donovani* (rarely by *L. tropica*). Kala-azar means 'black fever' in Hindi.

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Epidemiology

- Most cases of visceral leishmaniasis occur in Bangladesh, northeastern India (particularly Bihar state), Nepal, Sudan, and northeastern Brazil.
- Visceral leishmaniasis is transmitted by sandflies.
- It can also spread by blood transfusion or needle sharing.

Pathogenesis

- Infection begins in macrophages at the inoculation site as described above and disseminates throughout the reticuloendothelial system. Reticuloendothelial cells undergo hyperplasia which leads to enlargement of the spleen, liver and lymph nodes and bone marrow. Bone marrow infiltration, hypersplenism, autoimmune hemolysis, and bleeding all lead to pancytopenia.

Clinical Features

- The incubation period varies from weeks to months but can be as long as years.
- Males are affected more than females and children are affected more than adults.
- Patients usually present with intermittent fever (double quotidian) with rigors. Occasionally continuous fever can also occur.
- Skin manifestations in VL are frequent. Kala-azar means "black sickness" and refers to the earth-gray skin color in infected individuals.
- Hepatosplenomegaly is often present and splenomegaly can be massive. Lymphadenopathy is also present.
- Anemia is present in most patients due to hemolysis, hypersplenism and bone marrow suppression.
- Jaundice, hypoalbuminemia, edema and ascites can be there due to liver involvement.
- Death occurs due to secondary infections.

Diagnosis

- Kala-azar can be diagnosed by demonstration of the parasite in smears or cultures of a tissue aspirate or a biopsy specimen (e.g. of spleen, liver, bone marrow, or lymph node).
- Antibody detection by direct agglutination test (DAT) and ELISA are the tests of choice for field diagnosis.
- PCR is a sensitive test and can also identify the species. It can be performed on almost any tissue. It is not widely available.

Treatment

- Pentavalent antimonials (sodium stibogluconate) are the first-line drugs used to treat visceral leishmaniasis. Other choices include amphotericin B, pentamidine isotheonate and allopurinol. All these drugs are given parenterally.
- Recently miltefosine has been found to be highly effective and can be given orally. Sitamaquine, another oral agent, is also being field-tested.

Prevention

- Sandflies should be controlled by spraying DDT twice a year.
- Cases should be treated adequately to remove the reservoir of infection.
- Insecticide-impregnated mosquito net and repellants can be used for personal protection against sandfly bites.
- Vaccines are being developed.

Q. Post kala-azar dermal leishmaniasis (PKDL).

- Even after successful treatment of kala-azar, some people develop post kala-azar dermal leishmaniasis. This syndrome is manifested by skin lesions (macules, papules, nodules, and patches) which are most prominent on the face. The nodules can occur even on the tongue.
- In India, PKDL occurs one to several years after apparent cure. Parasites can be found in the skin lesions.
- Treatment for PKDL is same as for kala-azar but requires longer duration of treatment.

Q. Cutaneous leishmaniasis.

- Cutaneous leishmaniasis is caused by *L. tropica, L. major, L. aethiopica* and *L. mexicana.*

Clinical Features

- The first manifestation is usually a papule at the site of the sandfly bite. Papule becomes nodule and ulcerates with a central depression surrounded by a raised border. Secondary bacterial infection can happen to these lesions. The ulcer heals with a pigmented scar. Satellite lesions at the edge are common.

Diagnosis

- Histopathological examination of biopsy specimens from lesions can show amastigotes and exclude other diagnoses. Giemsa-stained smears of dermal scrapings, touch preparations of biopsy specimens can more easily identify amastigotes.

Treatment

- Some cases may heal spontaneously.
- Systemic therapy with antimonials is considered expensive and too toxic for cutaneous leishmaniasis. Local injection of antimonial is effective.

- Amphotercin B has been used in some trials and was found to be effective.
- Effective oral agents are miltefosine, fluconazole and itraconazole.

Q. Trypanosomiasis.

Q. American trypanosomiasis (Chagas' disease).

Q. African trypanosomiasis (sleeping sickness).

- Trypanosomiasis is caused by protozoans belonging to the genus *Trypanosoma.*
- There are mainly two types of trypanosomiasis, American trypanosomiasis and African trypanosomiasis.
- American trypanosomiasis (Chagas' disease) is caused by *Trypanosoma cruzi.* African trypanosomiasis (sleeping sickness) is caused by *Trypanosoma brucei gambiense* and *T. brucei rhodesiense*.

American Trypanosomiasis (Chagas' Disease)

- Chagas' disease is caused by the hemoflagellate protozoan *Trypanosoma cruzi*. *T. cruzi* is found only in America. It is the leading cause of congestive heart failure in areas of Latin America where it is endemic.

Pathogenesis

- It is transmitted to man by the bite of triatomines (a type of reduvid bug also known as kissing bug). These bugs ingest organisms while sucking blood from infected animals or humans. Ingested organisms multiply in the gut of the bugs, and infective forms are passed in the feces at the time of bite. Transmission occurs when breaks in the skin, mucous membranes, or conjunctivae become contaminated with bug feces.
- *T. cruzi* can also be transmitted by blood transfusion, organ transplantation and from mother to fetus.
- A nodular swelling or chagoma develops at the site of entry. Lymphatic spread then carries the organism to regional lymph nodes. When the histiocytes or other inflammatory cells ingest the parasites, they transform into amastigotes. After local multiplication, the organisms can assume the trypomastigote form and invade the bloodstream, carrying the infection to all parts of the body. Cells of the reticuloendothelial system, cardiac, skeletal, and smooth muscles, and neural cells are preferentially parasitized.
- During the acute phase of illness, the parasite is believed to directly destroy host cells. The pathogenesis of the cardiac and GI alterations typical of the chronic phase is not well characterized. Loss of ganglionic neurons and nerve fibers along with inflammatory reaction are important pathological findings.

Clinical Features

- An indurated inflammatory lesion called "chagoma" often appears at the site of parasite entry.
- If the bite occurs near the eye, unilateral painless edema of palpebrae and periocular tissues associated with preauricular lymphadenopathy (Romana's sign) occurs. These initial local signs are followed by malaise, fever, and anorexia.
- Cardiac abnormalities are the most frequent manifestations of chronic Chagas disease. Congestive heart failure is the first sign of chagasic heart disease. Other features are arrhythmias and heart blocks (commonly RBBB). Death usually occurs due to heart failure.
- Involvement of GI tract produces dysphagia, regurgitation, hiccups, constipation, and abdominal pain.
- Muscle involvement leads to myositis and myalgia.
- Nervous system involvement leads to meningoencephalitis.

Diagnosis

- Microscopic examination of anticoagulated blood or of the buffy coat can show the motile trypanosomes.
- Giemsa-stained blood smears can also show trypanosomes.
- Polymerase chain reaction (PCR) or blood culture in specialized media.
- Detection of specific antibodies.

Treatment

- There is no satisfactory treatment for Chagas' disease. Only two drugs—nifurtimox and benznidazole are available for treatment and both drugs lack efficacy and cause severe side effects. Nifurtimox, a nitrofurantoin derivative, is given for 3 or 4 months. New drugs are being developed.

African Trypanosomiasis (Sleeping Sickness)

Etiology

- African trypanosomiasis (sleeping sickness) is caused by *Trypanosoma brucei* complex, transmitted to man by the bite of tsetse flies. *Trypanosoma brucei gambiense* infection is prevalent in West Africa and *T. brucei rhodesiense* is prevalent in East Africa.

Life Cycle

- The tsetse fly becomes infected when it bites infected mammalian hosts. After multiplication in the midgut of the tsetse fly, the parasites migrate to the salivary glands. Parasites are transmitted to another mammalian host when the tsetse fly bites. The injected trypanosomes multiply in the blood of new host and invade all the organs causing illness.

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Clinical Features

- A painful chancre may appear in some patients at the site of bite associated with enlargement of the regional lymph nodes.
- Enlargement of the nodes of the posterior cervical triangle is known as 'Winterbottom's sign'.
- Hematogenous and lymphatic dissemination is marked by the onset of fever, headache, arthralgia, lymphadenopathy and hepatosplenomegaly.
- If untreated, CNS gets involved, producing sleepiness during the day (hence called sleeping sickness), night time insomnia, mental confusion, coma and death.
- In rhodesience infection, death from myocarditis and intercurrent infection can occur before sleeping sickness.

Diagnosis

- Microscopic examination of fluid expressed from the chancre or wet blood film may show trypanosomes. Thick and thin blood smears will also show trypanosomes. Concentration methods like centrifugation can be used if trypanosomes are not seen by the above methods. Lymph node aspirate and CSF can also show the parasites.
- Serological tests have not become popular because of variable sensitivity and specificity.
- PCR techniques are not yet commercially available.

Treatment

- The drugs traditionally used for treatment of African trypanosomiasis are suramin, pentamidine, and organic arsenicals (Melarsoprol and Tryparsamide). Eflornithine (difluoromethylornithine) is a recent addition. Treatment is individualized based on the infecting subspecies, the presence or absence of CNS disease and side effects.

Prevention

- Avoid areas which harbor tsetse flies, wear protective clothing and use insect repellents. Chemoprophylaxis is not recommended, and no vaccine is available at present.

Q. Babesiosis.

- Babesiosis is a tick-borne infectious disease caused by parasites of the genus *Babesia*. These protozoans are obligate parasites of red blood cells (RBCs). Wild and domestic animals are the natural reservoirs of *Babesia*. Transmission to humans is incidental.
- There are many species, but *Babesia microti* is responsible for most of the infections.

Epidemiology

- Most of the cases occur in the United States. Sporadic cases are reported in Europe and the rest of the world including India. The number of cases of *B. microti* illness has increased steadily over the last decade.

Life Cycle and Pathogenesis

- The nymphal stage of the deer tick *Ixodes scapularis* is the primary vector for transmission of *B. microti*. Transmission occurs from May through September with three-fourths of cases presenting in June and July. The incubation period is 1–6 weeks. Babesiosis can also be acquired through blood transfusion. There are case reports of congenital babesiosis also.

Clinical Features

- Patients present with a gradual onset of fever associated with chills, sweats, headache, myalgia, anorexia, dry cough, arthralgia, and nausea. Less common symptoms include neck stiffness, sore throat, shortness of breath, abdominal pain, and weight loss.
- Physical examination is usually normal except for fever. Occasionally, hepatosplenomegaly may be seen. Rarely jaundice, pharyngeal erythema, retinal infarcts, and retinopathy with splinter hemorrhages is seen.
- Severe babesiosis can occur in immunocompromised states such as asplenia, HIV/AIDS, malignancy, and immunosuppression. Complications such as ARDS, disseminated intravascular coagulation, congestive heart failure, and renal failure can occur in severe babesiosis. Splenic infarcts and rupture have also been reported.

Table 1.18 Treatment of African trypanosomiasis

Infecting species	Without CNS involvement	With CNS involvement
T. brucei gambiense (West Africa)	Suramin or eflornithine Alternative: Pentamidine	Eflornithine Alternative: Tryparsamide plus suramin
T. brucei rhodesiense (East Africa)	Suramin Alternative: Pentamidine	Melarsoprol

Diagnosis

- Babesiosis should be considered in patients who presents with flu-like symptoms and has recently resided in or traveled to an endemic area or received a blood transfusion.
- Babesiosis is diagnosed by microscopic examination of Giemsa-stained thin blood smears, on which *Babesia* species appear as round or pear-shaped organisms.
- If babesiosis is suspected but the parasite cannot be identified by microscopy, amplification of babesial rRNA by polymerase chain reaction (PCR) is recommended.
- Serology using indirect immunofluorescent antibody test is useful to confirm the diagnosis.

Treatment

- Treatment is indicated in symptomatic patients with positive *Babesia* tests.
- Mild *B. microti* illness: Oral atovaquone plus azithromycin for 7–10 days. Clindamycin plus quinine is the second choice.
- Severe *B. microti* illness: IV clindamycin plus oral quinine is given for 7–10 days.

Q. Toxoplasmosis.

- Toxoplasmosis is a disease caused by an intracellular parasite *Toxoplasma gondii*. Toxoplasmosis can be congenital or acquired.
- Congenital toxoplasmosis is transmitted from the mother to the fetus during pregnancy.
- Acquired infection is due to ingestion of cysts excreted in the feces of infected cats or from eating undercooked meat (especially lamb and pork).
- Infection can also be acquired through blood transfusion and organ transplantation.

Life Cycle and Pathogenesis

- The cat is the definitive host in which the sexual phase of the cycle takes place. Oocysts are formed in the cat and shed in feces. Vegetables or grass contaminated by cat feces can be ingested by animals, birds, and humans. Ingested oocysts become bradyzoites in the muscle of animals. Bradyzoites enter human intestine when they eat insufficiently cooked meat. Bradyzoites penetrate the small-intestinal epithelium and become tachyzoites. Tachyzoites can infect and multiply in all cells except RBCs. Multiplication continues until the cell ruptures, releasing parasites that infect adjoining cells. As a result of this, many tissues develop damage. In the congenital form of the disease, CNS, eyes, heart, lungs and adrenals are affected most often. In the acquired disease, the organism commonly involves lymph nodes and spleen and less commonly the liver and myocardium.

Clinical Features

- Majority of infections are asymptomatic.
- Congenitally infected children have neurologic complications such as hydrocephalus, microcephaly, mental retardation, chorioretinitis and epilepsy.

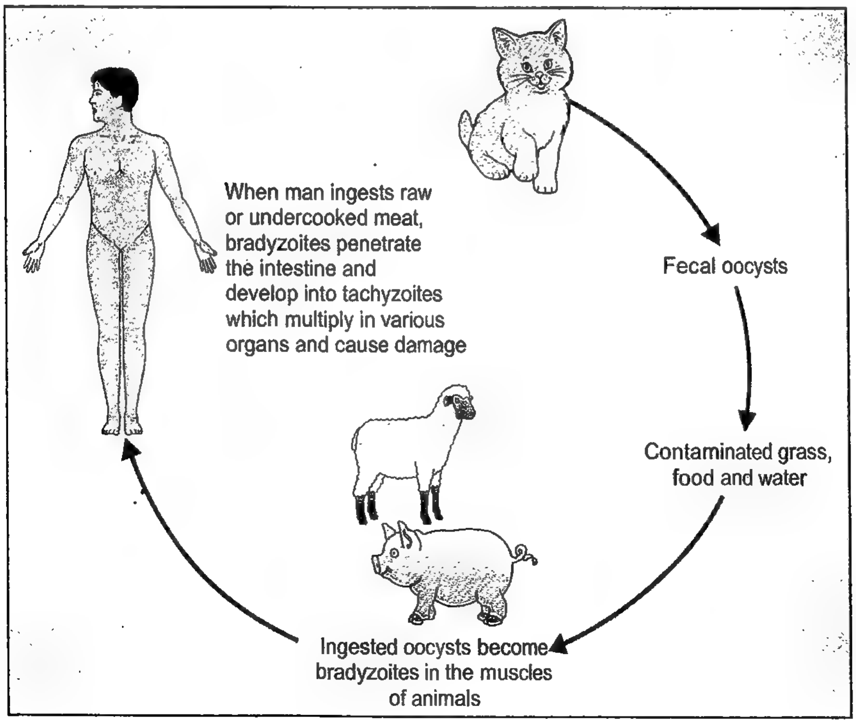

Fig. 1.14: Life cycle of toxoplasmosis

- Acquired infection presents with cervical lymphadenopathy with discrete, nontender lymph nodes. There may be fever, malaise, a maculopapular rash and hepatosplenomegaly (hence mistaken for infectious mononucleosis). Occasionally, uveitis, chorioretinitis, myocarditis and hepatitis can occur. Acquired infection can persist throughout life asymptomatically. In immunocompromised persons there may be encephalopathy, meningo-encephalitis, focal neurodeficits and cognitive dysfunction.

Investigations

- Serological tests like detection of antibodies are helpful in the diagnosis. A rise in the titre of IgM antibodies indicates acute infection. Antibodies persisting in an infant beyond 6 months of age imply congenital toxoplasmosis.
- Biopsy of a lymph node may show tachyzoites or histological changes.
- Body fluids or blood can be inoculated into the peritoneal cavity of mice and peritoneal fluid tested for organisms.
- Toxoplasma may be demonstrated in the CSF of immunocompromised patients.
- PCR techniques have high sensitivity and specificity and are recent developments.

Management

- Immunocompetent persons do not require specific treatment as the infection usually resolves spontaneously. But infants, immunosuppressed patients and those with eye involvement require treatment.
- A combination of pyrimethamine plus either sulfadiazine or clindamycin is used for treatment.
- For immunocompromised persons (such as HIV patients), trimethoprim-sulfamethoxazole (TMP-SMX) can be used as an alternative to above treatment. AIDS patients who are seropositive for *T. gondii* and who have a CD4+ T lymphocyte count of <100/µl should receive trimethoprim-sulfamethoxazole (TMP-SMX) as prophylaxis against toxoplasmosis.

Toxoplasmosis and Pregnancy

- If a seronegative woman acquires toxoplasmosis in first trimester of pregnancy, there is a high risk of fetal damage. Hence, termination of pregnancy should be considered in such women.
- If a woman is already seropositive before becoming pregnant, then there is no risk of fetal damage.
- Spiramycin 1 g qid for 4–6 weeks is safe for use during pregnancy.

Q. Describe the pathogenesis, clinical features, investigations and treatment of Pneumocystis infection.

Q. *Pneumocystis jiroveci* pneumonia (*Pneumocystis carinii*).

- *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) is an opportunistic fungal pulmonary pathogen and is an important cause of pneumonia in the immunocompromised individuals.
- Pneumocystis is now classified as a fungus. However, unlike fungi, Pneumocystis lacks ergosterol and is not susceptible to antifungal drugs.
- Pneumocystis has worldwide distribution and most people are exposed to the organism in childhood itself.

Pathogenesis

- Pneumocystis infection develops usually in immunocompromised individuals. HIV patients who have CD4+ counts below 200/µl have high chances of developing *Pneumocystis jiroveci* infection. Other persons at risk are patients on immunosuppressive therapy (particularly glucocorticoids) for cancer, organ transplantation, and other disorders; children with primary immunodeficiency diseases; and premature malnourished infants.
- After being inhaled, Pneumocystis reaches the alveoli, and attaches to type I alveolar cells. The main defence against Pneumocystis is alveolar macrophages, which ingest and kill the organism. If the immune system of the host is compromised, Pneumocystis multiplies and damages the type I alveolar cells, alters surfactant, and increases alveolar capillary permeability. Lung sections stained with hematoxylin and eosin, show the alveoli filled with a foamy exudate. In severe disease, there is interstitial edema, fibrosis, and hyaline membrane formation.

Clinical Features

- The incubation period is 1–2 months.
- Patients with pneumocystis pneumonia present with fever, dyspnea, and dry cough. Physical findings include tachypnea, tachycardia, and cyanosis, but there are a few lung findings (i.e. symptoms are more than signs). Pneumothorax may occur sometimes and management is difficult.
- Although pneumocystis usually remains confined to the lungs, disseminated infection can occur and involves lymph nodes, spleen, liver, and bone marrow. Eye lesions (choroiditis) also occur and may be confused with CMV retinitis.

Investigations

- *Chest X-ray* shows bilateral diffuse infiltrates mainly in the perihilar regions.
- *ABG (arterial blood gas)* analysis shows reduced arterial oxygen pressure (PaO_2), and respiratory alkalosis. There is increased alveolar–arterial oxygen gradient (PAO_2–PaO_2). PAO_2–PaO_2 of >35 mm Hg indicates poor prognosis.
- *Pulmonary function tests* show reduced diffusing capacity of the lung (DLCO) and an increased uptake of tracer with nuclear imaging (gallium-67 citrate scan).
- *Serum lactate dehydrogenase (LDH)* levels are usually elevated due to lung parenchymal damage.
- Since there is a little sputum production, sputum can be induced by inhalation of 3 percent saline and stained with *methenamine silver and toluidine blue* which selectively stain the wall of *P. carinii* cysts. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is more sensitive (>90%) than induced sputum.
- *Transbronchial biopsy and open lung biopsy* are performed only when the diagnosis remains in doubt.

Treatment

- Treatment should be started as soon as the diagnosis is suspected.
- Trimethoprim-sulphamethoxazole (TMP–SMX) is the drug of choice for all types of pneumocystis infections and is given for 14 days in non-HIV infected patients and 21 days in HIV infected patients. Other effective drugs include clindamycin, pentamidine and trimetrexate. Intravenous therapy may be switched over to oral after improvement.
- High-dose steroids improve the prognosis in HIV infected patients with pneumocystosis. However, one should be cautious about associated tuberculosis or fungal infection.

Prevention

- Primary prophylaxis is indicated for HIV-infected patients with CD4 counts less than 200 cells/cumm. Secondary prophylaxis is indicated for patients with prior pneumocystosis.
- TMP–SMX (one double strength tablet once daily) is the drug of choice. Dapsone (100 mg OD) is an alternative.

Q. Name the different tapeworms which infest human beings.

- Cestodes or tapeworms, are segmented worms.
- Adult worms reside in the gastrointestinal tract, but the larvae can be found in any organ.

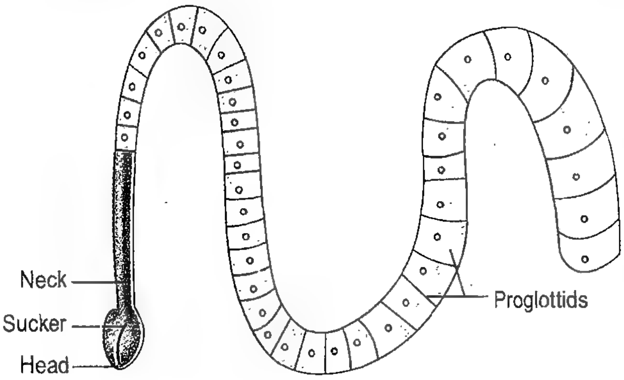

Fig. 1.15: Tapeworm

- Humans are either the definitive hosts where the adult worms reside in GIT (*Taenia saginata*, Diphyllobothrium, Hymenolepis, and *Dipylidium caninum*) or the humans are intermediate hosts where larval-stage parasites are present in the tissues (echinococcosis, sparganosis, and coenurosis).
- For *Taenia solium*, the human can be both definitive and intermediate host.
- An adult tapeworm consist of a head (scolex), a neck, and a chain of individual segments (proglottids). The scolex is the attachment organ through which tapeworm attaches to the intestinal mucosa. Neck is the narrow part behind scolex from which proglottids (segments) form. Proglottids are the segments. Mature proglottids produce eggs. Proglottids are hermophrodites and cross-fertilization between proglottids occurs. Big worms can be several metres in length. The entire worm is covered with an elastic cuticle. Tapeworms absorb nutrients directly through the cuticle since they do not have any GI tract.
- Five tapeworms commonly infect humans. These are:

Large tapeworms	Small tapeworms
Taenia saginata (beef tapeworm)	*Hymenolepis nana* (dwarf tapeworm)
Taenia solium (pork tapeworm)	*Echinococcus granulosis* (dog tapeworm)
Diphyllobothrium latum (fish tapeworm)	

Q. *Taenia saginata* (beef tapeworm).

- *T. saginata* (also called the cattle or beef tapeworm) occurs in all countries where raw or undercooked beef is eaten. This worm can reach 8 metres in length.

Life Cycle

- Humans are the only definitive host for the adult stage of *T. saginata* and cattle are intermediate hosts. It lives in the upper jejunum. It attaches to jejunal mucosa through a scolex which has four suckers. Eggs are passed

in the feces and can live for months to years on vegetation. Cattle may ingest these eggs while grazing. Inside the cattle intestine, the embryo is released which invades the intestinal wall, carried to striated muscle, where it becomes a cysticercus. When raw or undercooked beef is eaten by humans, this cysticercus can grow into adult worm.

Clinical Features

- Patients may notice worm segments (proglottids) in their feces. The proglottids are often motile.
- Abdominal pain or discomfort, nausea, decreased appetite, weakness, and weight loss can occur.

Diagnosis

- Detection of eggs or proglottids in the stool. Eggs may also be present in the perianal area; thus, if proglottids or eggs are not found in the stool, the perianal region should be examined with use of a cellophane-tape swab.
- Eosinophilia and elevated serum IgE levels may be present.

Treatment

- Praziquantel, given as a single dose (10 mg/kg), is effective against this tapeworm.

Prevention

- Proper cooking of beef and pork, inspection of beef before cooking, and proper disposal of human feces are measures which can prevent *T. saginata* infestation.

Q. *Taenia solium* and cysticercosis (pork tapeworm).

- *T. solium* is the pork tapeworm.
- It can cause two forms of infection. In humans, infection can be with adult tapeworm in the intestine or with larval forms in the tissues (cysticercosis).
- It has worldwide distribution.

Life Cycle

- Humans are the only definitive hosts for *T. solium*; pigs are the usual intermediate hosts. The adult tapeworm usually stays in the upper jejunum. It has a scolex with two sucking disks through which it attaches to the mucosa. The adult worm is about 3 m in length and may live for years. Proglottids (segments) contain eggs and are passed in the feces. Eggs can survive in the environment for many months. These eggs are infective to humans and animals. If eggs are ingested by animals and man, the larvae are released in the intestine, penetrate the intestinal wall, and are carried to many tissues. In the tissues, larvas become encysted in 2–3 months (cysticerci). These cysticerci can survive for months to years. Humans also acquire infection by ingesting undercooked pork containing cysticerci. In this case ingested cysticerci develop into adult tapeworms in the intestine. Autoinfection may occur if an individual ingests eggs from his own feces.

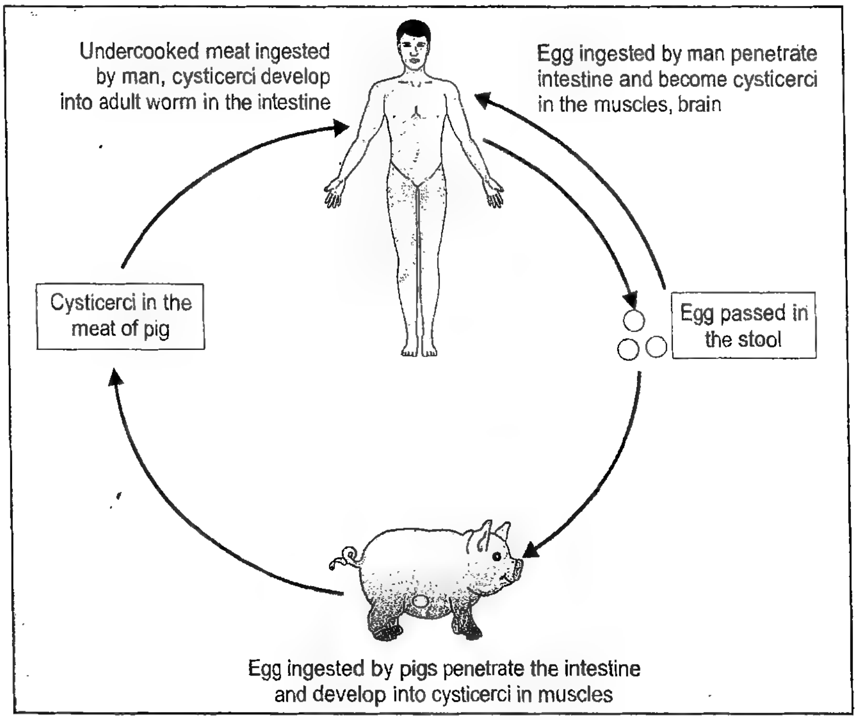

Fig. 1.16: Life cycle of *Taenia solium*

Clinical Manifestations

- Intestinal infection with *T. solium* is usually asymptomatic or produces epigastric discomfort, nausea, weight loss, and diarrhea. Worm segments (proglottids) may be noted in feces.
- In cysticercosis, the clinical manifestations depend on the location of cysticerci. Cysticerci are commonly found in the brain, skeletal muscle, subcutaneous tissue, and eye.
- Cysticerci in the brain act like space occupying lesions. Seizures, hydrocephalus (due to obstruction of CSF flow by cysticerci), signs of raised intracranial pressure, including headache, nausea, vomiting, changes in vision, dizziness, ataxia, or confusion, may be present. Patients with hydrocephalus may develop papilledema or display altered mental status. Chronic meningitis and strokes can also occur.
- In the eye they may cause blindness.

Diagnosis

- Stool examination may show eggs or worm segments.
- Definitive diagnosis of cysticercosis is difficult because it requires biopsy and histopatholgical studies which are sometimes difficult to obtain as in brain infection. However, a clinical diagnosis can be made based on clinical features, imaging studies, serologic tests, and exposure history.

Treatment

Intestinal Infection

- Praziquantel (10 mg/kg) as a single dose is effective. Niclosamide (2 g) is an alternative.

Neurocysticercosis

- Praziquantel 50 to 60 mg/kg daily in three divided doses for 15 days or albendazole (15 mg/kg per day for 8 to 28 days) hasten the resolution of cysticercosis.
- Both drugs can exacerbate the inflammatory response due to dying parasite, which may be prevented by addition of steroids.
- Antiepileptics for seizures.
- Obstructive hydrocephalus is treated by the removal of the cysticercus via endoscopic surgery or by ventriculoperitoneal shunting.

Prevention of *T. solium* Infection

- Same as for *T. saginata* infection.

Q. Diphyllobothriasis.

- *Diphyllobothrium latum* (fish tapeworm) and other Diphyllobothrium species are found in lakes and rivers.

Life Cycle

- The adult tapeworm (this is the longest tapeworm, grows up to 12 meters) lives usually in the ileum and occasionally in the jejunum. The adult worm has 3000 to 4000 proglottids (segments) which release eggs daily into the feces. If an egg reaches water, it hatches and releases a free-swimming embryo which is eaten by cyclops. Inside the cyclops the embryo develops into a procercoid which is swallowed by a fish. Inside the fish, the larva migrates into the fish's flesh and grows into a sparganum larva. Humans acquire the infection by ingesting infected raw fish. Inside the human intestine, the larva matures into an adult worm.

Clinical Manifestations

- Most *D. latum* infections are asymptomatic. Some may have abdominal discomfort, diarrhea, vomiting, weakness, and weight loss. Rarely worm can cause intestinal obstruction, cholangitis or cholecystitis. Because the tapeworm absorbs vitamin B_{12}, vitamin B_{12} deficiency can develop which manifests as megaloblastic anemia.

Diagnosis

- Stool examination may show eggs or worm segments (proglottids) in the stool. Eosinophilia may be present.

Treatment

- Praziquantel, 5 to 10 mg/kg as a single dose is highly effective.

Q. *Hymenolepis nana* (dwarf tapeworm).

- This is the most common and smallest tapeworm (2 cm in length) infesting human beings. *H. nana* is endemic all over the world. Infection is spread by fecooral contamination.

Life Cycle

- *H. nana* is the only tapeworm which does not require an intermediate host. Both the larval and adult phases take place in the human. The adult worm resides in the proximal ileum. The eggs are released into the feces and when ingested by a new host, the oncosphere is freed and penetrates the intestinal villi, becoming a cysticercoid larva. Larva migrates back into the intestinal lumen, attaches to the mucosa, and matures into adult worm. Eggs may also hatch before passing into the stool, causing internal autoinfection

Clinical Manifestations

- Infection is usually asymptomatic. Occasionally anorexia, abdominal pain, and diarrhea may be seen.

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Diagnosis

- Detection of eggs in the stool.

Treatment

- Praziquantel (25 mg/kg once) is the drug of choice. It is effective against both the adult worms and the cysticercoids.

Q. Echinococcosis (dog tapeworm) (hydatid cyst).

- Echinococcosis is an infection caused in humans by the larval stage of *Echinococcus granulosus, E. multilocularis,* or *E. vogeli.*
- *E. granulosus* produces unilocular cystic lesions. *E. multilocularis* causes multilocular lesions. *E. vogeli* causes polycystic hydatid disease.

Life Cycle

- Like other cestodes, echinococcal species have both intermediate and definitive hosts. The definitive hosts are dogs that pass eggs in their feces. These eggs are ingested by intermediate hosts—sheep, cattle, humans, goats, camels, and horses either through vegetables or while grazing. Eggs develop into cysts in the muscles of intermediate hosts. When a dog ingests beef or lamb containing cysts, they develop into adult worms in dogs and life cycle is completed.
- When humans ingest the eggs, embryos escape from the eggs, penetrate the intestinal mucosa, enter the portal circulation, and are carried to various organs, most commonly the liver and lungs where they develop into fluid-filled unilocular hydatid cysts. These cysts consist of an external membrane and an inner germinal layer. Daughter cysts and brood capsules develop from the inner germinal layer. New larvae, called protoscolices, develop within the brood capsule. The cysts expand slowly over a period of years.
- The life cycle of *E. multilocularis* is the same except that the intermediate hosts are rodents.

Clinical Manifestations

- Echinococcal cysts remain asymptomatic until their expanding size elicits symptoms in the involved organ. Liver and lungs are involved commonly. Patients with liver cysts often present with abdominal pain or a palpable mass in the right upper quadrant. Compression of a bile duct can cause biliary obstruction and jaundice. Involvement of bone leads to pathologic fractures, CNS involvement leads to seizure, neurological deficits and raised ICT. Involvement of the heart leads to conduction defects and pericarditis.
- Rupture or leakage of hydatid cyst fluid may produce fever, pruritus, urticaria, eosinophilia, or anaphylaxis. Lung hydatid cysts may rupture into the bronchi or peritoneal cavity and produce cough, chest pain, or hemoptysis. Rupture of hydatid cysts may lead to dissemination of protoscolices, which can develop into additional cysts. Rupture can occur spontaneously or at surgery.

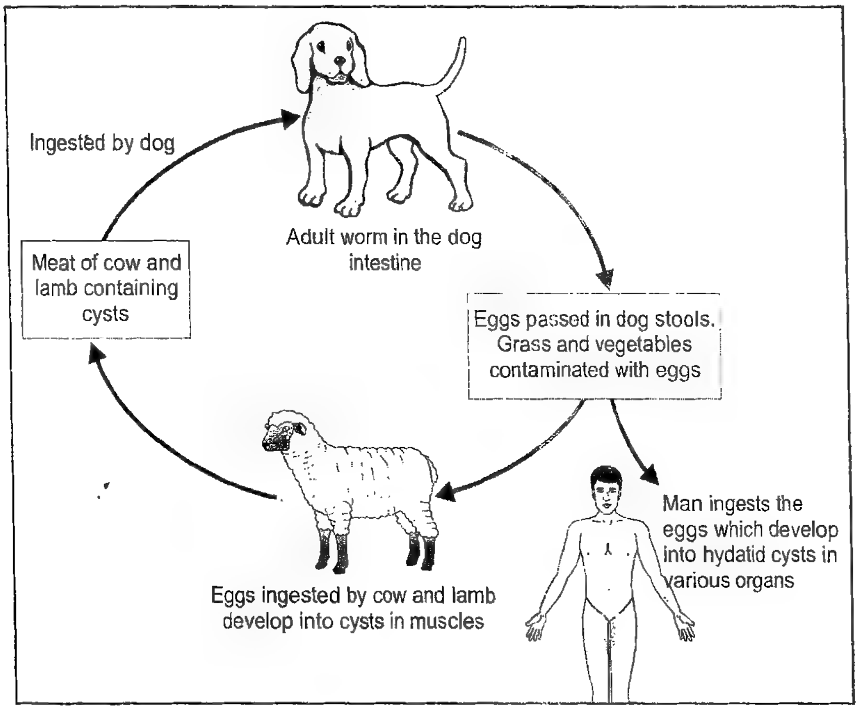

Fig. 1.17: Life cycle of dog tapeworm (hydatid cyst)

- The larval forms of *E. multilocularis* present as slowly growing mass in the liver with destruction of hepatic parenchyma. These cysts may lead to obstruction of biliary tree leading to obstructive jaundice, or invade adjacent structures like diaphragm, kidneys and lungs.

Diagnosis

- MRI, CT, and ultrasound can define the site and size of echinococcal cysts.
- Examination of aspirated fluid from cyst for protoscolices or hooklets can make a definite diagnosis of *E. granulosus* infection, but is not usually recommended because of the risk of fluid leakage resulting in either dissemination of infection or anaphylactic reactions.
- Serologic studies for antibodies can be useful, but negative result does not rule out the diagnosis.

Treatment

- For uncomplicated *E. granulosus* cysts, PAIR (percutaneous aspiration, infusion of scolicidal agents, and reaspiration) is now the treatment of choice. PAIR is contraindicated for superficially located cysts (because of the risk of rupture), for cysts with multiple internal septae, and for cysts communicating with the biliary tree. Albendazole (15 mg/kg daily in two divided doses) should be given for at least 4 days before the procedure and continued for at least 4 weeks afterward.
- For complicated *E. granulosus* cysts (e.g. those communicating with the biliary tree), surgery is the treatment of choice. Pericystectomy is the procedure of choice, where the entire cyst and the surrounding fibrous tissue are removed. There is a risk of spillage of cyst contents during surgery. Albendazole should be given for several days before resection and for several weeks after resection. Praziquantel (50 mg/kg daily for 2 weeks), may hasten the death of the protoscolices.
- Medical therapy with albendazole alone for 12 weeks to 6 months results in cure in ~30% of cases and improvement in another 50%.
- Surgical resection remains the treatment of choice for *E. multilocularis* infection.

Q. Name the different intestinal nematodes that infest man.

Intestinal Nematodes

- Intestinal nematodes are roundworms. Their length varies from 1 mm to many centimeters. There are more than a billion people worldwide who are infected with intestinal nematodes. Though nematode infections are not usually fatal, they can cause malnutrition and diminished work capacity.

Table 1.19 Intestinal nematodes infesting man

	***Ascaris lumbricoides* (Roundworm)**	**Hookworm (*Necator americanus, Ancylostoma duodenale*)**	***Strongyloides stercoralis***	***Trichuris trichiura* (Whipworm)**	***Enterobius vermicularis* (Pinworm)**
Endemic areas	Worldwide	Hot, humid regions	Hot, humid regions	Worldwide	Worldwide
Infective stage	Egg	Filariform larva	Filariform larva	Egg	Egg
Route of infection	Oral	Percutaneous	Percutaneous	Oral	Oral
Gastrointestinal location of worms	Jejunum	Jejunum	Small intestine	Cecum, colon	Cecum, appendix
Adult worm size	15–40 cm	0.7–1.2 cm	2 mm	3–5 cm	0.8–1.3 cm
Pulmonary passage of larvae	Yes	Yes	Yes	No	No
Incubation period (days)	60–75	40–100	17–28	70–90	35–45
Lifespan	1–2 years	2–8 years	Decades (owing to autoinfection)	5 years	2 months
Main symptoms	Usually asymptomatic. Rarely gastrointestinal or biliary obstruction	Iron-deficiency anemia	Gastrointestinal symptoms, malabsorption	Gastrointestinal symptoms, anemia	Perianal pruritus
Diagnosis	Detection of eggs in stool	Detection of eggs in fresh stool larvae in old stool	Detection of larvae in stool or duodenal aspirate	Detection of eggs in stool	Detection of eggs from perianal skin on cellulose acetate tape
Treatment	Mebendazole Albendazole Pyrantel pamoate	Mebendazole Pyrantel pamoate Albendazole	Ivermectin Albendazole Thiabendazole	Mebendazole Albendazole	Mebendazole Pyrantel pamoate Albendazole

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Q. Describe the life cycle, clinical features, diagnosis and treatment of intestinal ascariasis.

- Ascaris is a nematode seen worldwide.
- It is transmitted through fecooral route and is common in areas of poor sanitation.
- *Ascaris lumbricoides* can reach up to 40 cm in length.

Life Cycle

- Adult worms live in the small intestine for 1 to 2 years. Female Ascaris worms produce eggs which are passed in the stools. These eggs mature in the soil and become infective after several weeks. Eggs can remain infective for many years. When a person swallows these eggs, eggs hatch in the intestine and produce larvae. These larvae invade the intestinal mucosa, reach lungs through circulation, break into the alveoli, ascend the bronchial tree, and are swallowed. They reach small intestine and develop into adult worms. About 2 and 3 months are required from swallowing of eggs to development of adult worms.

Clinical Features

- Most infected individuals are asymptomatic. Symptoms arise due to larval migration through the lungs or adult worms in the intestines.
- When the larvas migrate through the lungs, patients may develop a dry cough and burning substernal discomfort worsened by coughing or deep inspiration. Sometimes dyspnea and blood-tinged sputum may be seen. Low grade fever and weight loss may be present. All these features may be mistaken for pulmonary tuberculosis. Eosinophilia develops during this symptomatic phase and subsides slowly over weeks. Chest X-rays may show eosinophilic pneumonitis (Löffler's syndrome), with round or oval infiltrates.
- In heavy infections, a large number of worms can get entangled and cause intestinal obstruction. Single worms may migrate into and occlude the biliary tree, causing biliary colic, cholecystitis, cholangitis, and pancreatitis. Sometimes worms may come out of mouth or nose.

Diagnosis

- Detection of Ascaris eggs in the stool sample.
- Detection of larvae in sputum or gastric aspirates when they migrate through the lungs.
- Eosinophilia may be found in the blood in early stages.
- The large adult worm shadows may be visualized, occasionally on contrast studies of the gastrointestinal tract. A plain abdominal X-ray may show masses of worms in gas-filled loops of bowel in patients with intestinal obstruction.
- Pancreaticobiliary worms can be detected by ultrasound and endoscopic retrograde cholangiopancreatography (ERCP).

Treatment

- Albendazole (400 mg once), or mebendazole (500 mg once) is effective against ascariasis. These drugs are contraindicated in pregnancy and instead pyrantel pamoate (11 mg/kg once; maximum, 1 g) can be used in pregnancy. Intestinal obstruction requires surgery.

Q. Describe the epidemiology, life cycle, clinical features, diagnosis and treatment of hookworm infestation.

Epidemiology

- Human hookworm disease is predominantly caused by the nematode parasites *Necator americanus* and *Ancylostoma duodenale*; and rarely by *Ancylostoma ceylonicum, Ancylostoma braziliense*, and *Ancylostoma caninum*.
- *Ancylostoma duodenale* is found in Mediterranean countries, Iran, India, Pakistan, and the Far East. *Necator americanus* is found in North and South America, Central Africa, Indonesia, and parts of India. Both are found in many tropical regions, particularly Southeast Asia.
- It is common in rural areas where defecating in open fields is common. Barefoot walking is a risk factor for infection.
- Older children are affected commonly.
- *Ancylostoma caninum* and *Ancylostoma braziliense* are animal hookworms and can cause cutaneous larva migrans ("creeping eruption").

Life Cycle

- Adult hookworms are ~1 cm long. They attach to the intestinal mucosa through buccal teeth (ancylostoma) or cutting plates (necator) and suck blood (0.5 ml/day per ancylostoma adult and 0.03 ml/day per each *N. americanus*) and interstitial fluid. The adult hookworms produce thousands of eggs daily. The eggs are passed with feces into the soil, where rhabditiform larvae hatch and develop over a 1-week period into filariform larvae. These filariform larvae penetrate the skin and reach the lungs through bloodstream. In the lungs, they invade alveoli and ascend the airways, get swallowed and reach the small intestine. In the small intestine they develop into adult worms. It takes about 6 to 8 weeks from skin invasion to appearance of eggs in the feces. Adult hookworms live about 6 to 8 years (*A. duodenale*) or 2 to 5 years (*N. americanus*).

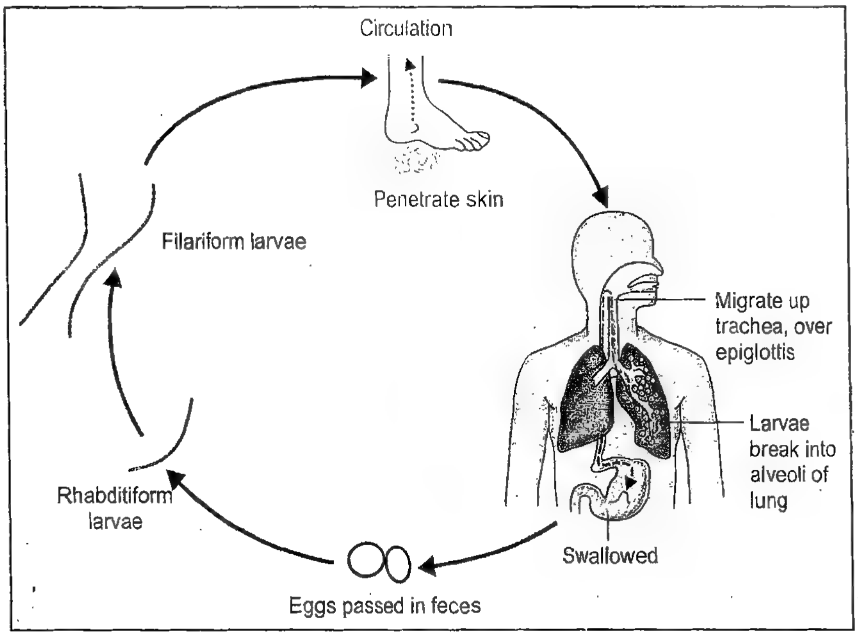

Fig. 1.18: Life cycle of hookworm

Clinical Features

- Most hookworm infections are asymptomatic.
- Filariform larvae may cause pruritic maculopapular dermatitis ("ground itch") at the site of skin penetration as well as serpiginous tracks when they migrate through subcutaneous tissue (similar to cutaneous larva migrans).
- Larvae migrating through the lungs may cause transient pneumonitis.
- Mild epigastric pain or diarrhea may be seen sometimes.
- Chronic hookworm infection leads to iron deficiency anemia.

Diagnosis

- Detection of oval hookworm eggs in the feces. In light infections, stool-concentration procedures may be required to detect eggs. Eggs of the two species cannot be differentiated by light microscopy.
- Eosinophilia may be present.
- Microcytic hypochromic anemia, occasionally with eosinophilia is characteristic of chronic hookworm infestation.

Treatment

- Albendazole (400 mg single dose), or mebendazole (500 mg single dose), or pyrantel pamoate (11 mg/kg for 3 days) are highly effective.

Q. Strongyloidiasis.

- Strongyloidiasis is due to *Strongyloides stercoralis* which is a helminth.
- In contrast to other helminthic parasites, *S. stercoralis* can complete its entire life cycle within the human host. This unique capacity leads to repeated cycles of autoinfection and thus strongyloidiasis can persist for decades in the host.

Epidemiology

- *S. stercoralis* is found in tropical areas and is particularly common in Southeast Asia, sub-Saharan Africa, and Brazil. It is also found in some parts of the United States.

Life Cycle

- Adult female worms of *S. stercoralis* are about 2 mm long. Parasitic adult males do not exist and female worms produce eggs by parthenogenesis. Eggs hatch in the intestine itself, releasing rhabditiform larvae which are passed with the feces into soil. These rhabditiform larvae transform into infectious filariform larvae either directly or after a free-living phase of development in the soil. Humans acquire strongyloidiasis when filariform larvae penetrate the skin or mucous membranes and enter the body. These filariform larvae reach the lungs through bloodstream. In the lungs, they invade alveoli and ascend the airways, get swallowed and reach the small intestine. In the small intestine, larvae mature into adult worms that penetrate the mucosa of the small intestine. Alternatively, rhabditiform larvae in the intestine can develop directly into filariform larvae that penetrate the colonic wall or perianal skin and enter the blood stream to repeat the migration that establishes ongoing internal reinfection (autoinfection).

Clinical Features

- Most patients are asymptomatic or have mild cutaneous and/or abdominal symptoms.
- Recurrent urticaria is the most common cutaneous manifestation.
- Migrating larvae can elicit a pathognomonic serpiginous eruption, larva currens ("running larva"), a pruritic, raised, erythematous lesion that advances as rapidly as 10 cm/h along the course of larval migration.
- Adult worms burrow into the duodenojejunal mucosa and can cause abdominal (usually epigastric) pain, which resembles peptic ulcer pain. Nausea, diarrhea, gastrointestinal bleeding, and weight loss can occur.
- Immunosuppressed states can lead to disseminated infection where larvae may invade the central nervous system, peritoneum, liver, and kidney.

Diagnosis

- Finding rhabditiform larvae in feces is diagnostic. Since the eggs hatch in the intestine, they are not usually found in the feces. Repeated stool examinations can improve the sensitivity of stool diagnosis.
- If stool examinations are negative, strongyloides can be detected by sampling of the duodenojejunal contents by aspiration or biopsy.
- Detection of antibodies against Strongyloides is a sensitive method of diagnosing uncomplicated infections.
- Eosinophilia is common.

Treatment

- Ivermectin (200 µg/kg daily for 1 or 2 days) is the drug of choice and is more effective than albendazole (400 mg daily for 3 days, repeated at 2 weeks) and is better tolerated than thiabendazole (25 mg/kg twice daily for 2 days). Ivermectin should be given for at least 5 to 7 days in disseminated strongyloidiasis.

Q. Trichuriasis (whipworm).

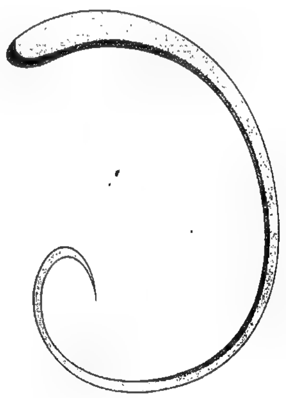

Fig. 1.19: Whipworm

- Trichuriasis is caused by infection with the nematode, *Trichuris trichiura*.
- It is about 4 cm long and has a thin anterior end and a broad posterior end which gives it a characteristic whiplike appearance (hence called whipworm).

Epidemiology

- It is found all over the world both in the tropics and subtropics.
- It most commonly affects poor children.

Life Cycle

- The adult worms live for many years in the colon and cecum. Their anterior ends are embedded into the mucosa. Adult female worms produce thousands of eggs per day which are passed with the feces, mature in the soil and become infective. After ingestion, infective eggs hatch in the duodenum, releasing larvae which mature and migrate to the colon. The full cycle takes about 3 months.

Clinical Features

- Most infected persons are asymptomatic.
- Heavy infections can cause abdominal pain, anorexia, and diarrhea. Rectal prolapse and growth retardation can happen in children.

Diagnosis

- The characteristic lemon-shaped whipworm eggs may be detected on stool examination. Adult worms can occasionally be seen on proctoscopy.

Treatment

- Mebendazole (500 mg once for mass treatment or 100 mg BD for 3 days for individual patient) or albendazole (400 mg daily for 3 doses) are effective against whipworm.

Q. Enterobiasis (pinworm).

- *Enterobius vermicularis* is a small nematode ~1 cm long. It is more common in temperate countries than in the tropics. Schoolchildren are affected more commonly.

Life Cycle

- Humans are the only natural host for enterobius. Adult worms live in the terminal ileum and colon. The female worm migrates out at night into the perianal region and lays up to 10,000 eggs. Self-infection results from perianal scratching and transport of eggs by the hands to the mouth. The larvae hatch and mature within the intestine. This life cycle takes ~1 month, and adult worms live for ~2 months. It can spread easily from one person to another.

Clinical Features

- Most pinworm infections are asymptomatic. Perianal itching is the cardinal symptom. The itching is worse at night and is due to the nocturnal migration of the female worms.
- Heavy infections can cause abdominal pain and weight loss.
- Rarely, pinworms invade the female genital tract and cause vulvovaginitis.

Diagnosis

- Since the eggs are deposited in the perianal region, they can be detected by the application of clear cellophane tape to the perianal region in the morning. Eggs get attached to the sticky cellophane tape which is then transferred to a slide and examined under microscope for characteristic pinworm eggs, which are oval and flattened along one side.

Treatment

- A single dose of mebendazole (100 mg), or albendazole (400 mg), or pyrantel pamoate (11 mg/kg base), is effective against pinworms. Treatment should be repeated after 2 weeks. All family members should be treated to eliminate asymptomatic reservoirs of infection.

Q. Enumerate the different filarial species which cause infection in man.

- Filariasis is a group of parasitic infections due to filarial worms (nematodes) (Table 1.20). World Health Organization (WHO) has identified lymphatic filariasis as the second leading cause of permanent and long-term disability in the world, after leprosy.
- Filariasis is transmitted by mosquitoes or other arthropods.
- Eight filarial species infect humans. Out of these, four are:
  1. *Wuchereria bancrofti*
  2. *Brugia malayi*
  3. *Onchocerca volvulus*, and
  4. *Loa loa*—are responsible for most infections.
- Adult filarial worms reside in either lymphatic or subcutaneous tissues of humans. Adult worms live for many years and produce offsprings called microfilariae, which either circulate in the blood or migrate through the skin.
- Microfilariae are ingested by the arthropod vector and there develop into new infective larvae.
- All filarial worms have similar life cycles but differ in: (1) their vector, (2) the final dwelling place of the adult worms, (3) the circadian periodicity of the microfilariae, and (4) the pathological syndromes they cause.

Q. Describe the etiology, epidemiology, pathogenesis, clinical features, diagnosis and treatment of lymphatic filariasis.

Q. *Wuchereria bancrofti*.

- Lymphatic filariasis is caused by *W. bancrofti, B. malayi*, or *B. timori*. The thread-like adult worms live in lymphatic channels or lymph nodes for many years.

Epidemiology

- *W. bancrofti* is the most common human filarial infection seen all over the world. Humans are the only definitive host for this parasite. *W. bancrofti* is nocturnally periodic except in Pacific Islands where they are subperiodic. (Nocturnal periodicity means microfilariae are found in peripheral blood mainly at night, whereas subperiodicity means microfilarias are present in peripheral blood at all times). Vectors for *W. bancrofti* are culex fatigans mosquitoes in urban settings and anopheles or aedes mosquitoes in rural areas.
- *B. malayi* occurs mainly in China, India, Indonesia, Korea, Japan, Malaysia, and the Philippines.

Table 1.20 Filarial species causing disease in humans

Worm species	Periodicity	Vector	Dwelling place of adult worm	Dwelling place of microfilariae
Wuchereria bancrofti	Nocturnal	Mosquitoes	Lymphatic vessels	Blood
Brugia malayi	Nocturnal	Mosquitoes	Lymphatic vessels	Blood
B. timori	Nocturnal	Mosquitoes	Lymphatic tissue	Blood
Oncocercus valvulus	None	Simulium (blackflies)	Subcutaneous	Skin
Loa loa	Diurnal	Chrysops (deerflies)	Subcutaneous	Blood
Mansonella ozzardi	None	Midges	Retroperitoneal	Blood and skin
Mansonella perstans	None	Midges	Retroperitoneal	Blood
Mansonella streptocerca	None	Midges	Skin	Skin

- *B. timori* is seen only on islands of the Indonesian archipelago.

Pathology

- Adult worms live in afferent lymphatics or sinuses of lymph nodes and cause dilatation and thickening of lymphatics. An inflammatory reaction develops in the lymphatics due to the presence of worms which further damages lymphatics and their valves leading to tortuous and blocked lymphatics. Blocked and damaged lymphatics lead to lymphedema with hard or brawny edema in the overlying skin. Death of the adult worm leads to increased inflammatory reaction and fibrosis of lymphatics which may be permanent.
- Microfilariae do not have much role in the development of lymphadema.

Clinical Features

- Patients with lymphatic filariases usually present with subclinical microfilaremia, hydrocele, acute adenolymphangitis (ADL), and chronic lymphatic disease.
- In areas where *W. bancrofti* or *B. malayi* is endemic, most infected individuals are clinically asymptomatic. Investigations may show microfilariae in the blood or microscopic hematuria and/or proteinuria, dilated and tortuous lymphatics on imaging. Scrotal lymphangiectasia may be detectable by ultrasound.
- Only very few of these asymptomatic individuals develop acute and chronic stages of infection. ADL is characterized by fever, lymphangitis, lymphadenitis, and transient local edema. Lymphangitis is inflammation of lymphatic vessels and is retrograde extending from the lymph node to periphery. In bacterial lymphangitis ascending lymphangitis is seen. Lymphadenitis is inflammation of lymph nodes which become enlarged and painful. The lymphangitis and lymphadenitis can involve both the upper and lower limbs. Severe lymphatic damage can lead to permanent changes associated with elephantiasis. Initially there is pitting edema, which becomes nonpitting later due to thickening of the subcutaneous tissues and hyperkeratosis. Recurrent infections of these edematous tissues lead to further swelling.
- Genital lymphatics involvement occurs almost exclusively with *W. bancrofti* infection and manifests as funiculitis, epididymitis, and scrotal pain and tenderness. Hydroceles and scrotal elephantiasis may develop. Renal lymphatic involvement leads to rupture of the renal lymphatics and chyluria.

Diagnosis

- Definitive diagnosis can be made by detection of adult filarial worms. But this is difficult. Imaging techniques like ultrasound and Doppler can sometimes identify motile adult worms in the dilated lymphatics.
- Microfilariae can be demonstrated in the blood, hydrocele fluid, or rarely in other body fluids. Blood should be collected based on the periodicity of the microfilariae. Night time blood sample should be examined in case of nocturnal periodicity.
- Antigens of *W. bancrofti* can be detected by enzyme-linked immunosorbent assay (ELISA) and immunochromatographic card test. There are currently no tests to detect antigens of brugian filariasis.
- Polymerase chain reaction (PCR)–based assays for DNA of *W. bancrofti* and *B. malayi* in blood have been developed. PCR tests have high sensitivity and can detect infection in almost all infected subjects.
- Radionuclide lymphoscintigraphic imaging of the limbs can show lymphatic abnormalities, but not used clinically and is mainly a research tool.
- Elevated eosinophils, serum IgE, and antifilarial antibody support the diagnosis of lymphatic filariasis.

Differential Diagnosis

- Acute filarial lymphangitis and lymphadenitis has to be differentiated from bacterial lymphangitis.
- Chronic filarial lymphedema must be distinguished from the lymphedema of malignancy, postoperative scarring, trauma, chronic edematous states, and congenital lymphatic abnormalities.

Treatment

- Diethylcarbamazine (DEC) is the drug of choice for filariasis. It has action on adult worms as well as microfilariae. It is given in a dose of 6 mg/kg/day in three divided doses for 2 to 3 weeks. A single dose of 6 mg/kg also has equivalent efficacy in reducing levels of microfilariae.
- Ivermectin is a semisynthetic macrolide antibiotic and a single oral dose of 150 mcg/kg is as effective as a 12-day course of DEC.
- Combination of single doses of albendazole and either DEC or ivermectin have been found to be more effective than single drug.
- Early treatment of asymptomatic persons is recommended to prevent permanent lymphatic damage. For ADL, supportive treatment with antipyretics and analgesics is given and antibiotics are also indicated if secondary bacterial infection is suspected. In persons who have chronic lymphadema, good local hygiene should be

maintained, and secondary bacterial infections should be prevented. Hydroceles are managed by repeated aspiration or surgical intervention.

Prevention and Control

- Avoidance of mosquito bites by using insect repellents and mosquito nets reduce the chances of infection.
- Mass treatment with either DEC or ivermectin every year suppress microfilaremia and interrupts transmission.
- Community use of DEC-fortified salt dramatically reduces microfilarial density.

Q. Tropical pulmonary eosinophilia.

- Tropical pulmonary eosinophilia (TPE) is a distinct syndrome that develops in some individuals with lymphatic filariasis.
- Males are affected commonly often during the third decade of life. Most cases occur in India, Pakistan, Sri Lanka, Brazil, and Southeast Asia.

Clinical Features

- Patients are usually from filaria-endemic areas.
- They usually present with nocturnal dry cough and wheezing (probably due to the nocturnal periodicity of microfilariae), weight loss, low-grade fever, and high blood eosinophil counts (usually >3000 eosinophils/µl).
- The clinical symptoms are due to allergic and inflammatory reactions elicited by the microfilariae in the lungs.
- Interstitial fibrosis and lung damage can happen if this condition is not treated properly.

Investigations

- Eosinophil count is high (usually >3000 eosinophils/µl).
- Chest X-ray may show increased bronchovascular markings, diffuse miliary lesions or mottled opacities.
- Pulmonary function tests show both restrictive and obstructive defects.
- Serum IgE levels and antifilarial antibodies are elevated.

Differential Diagnosis

- Asthma
- Allergic bronchopulmonary aspergillosis
- Löffler's syndrome
- Allergic granulomatosis with angiitis (Churg-Strauss syndrome)
- Systemic vasculitis (Wegener's granulomatosis)
- Chronic eosinophilic pneumonia
- Idiopathic hypereosinophilic syndrome.
- H/o of filarial exposure, nocturnal cough and wheezing, high levels of antifilarial antibodies, and a rapid response to DEC help in differentiating TPE from other conditions.

Treatment

- DEC should be given at a dosage of 4 to 6 mg/kg of body weight divided into 2 or 3 doses per day for 14 days.

Q. Onchocerciasis (river blindness).

- Onchocerciasis (river blindness) is caused by the filarial nematode onchocerca volvulus. Humans acquire onchocerciasis through the bite of *simulium* blackflies. Because the fly develops and breeds in flowing water, onchocerciasis is commonly found along rivers and is sometimes referred to as river blindness.
- This disease is seen mainly in Africa.
- It affects mainly the skin, eyes, and lymph nodes. Onchocerciasis is the second leading cause of infectious blindness worldwide.

Life Cycle and Pathogenesis

- Man acquires infection by the bite of an infected blackfly. Infective larvae of *O. volvulus* are deposited into the skin during bite. The larvae develop into adults worms, which are found in subcutaneous nodules. The adult female worm releases microfilariae that migrate to all tissues. Infection is transmitted to other persons when a female blackfly ingests microfilariae from the host and these microfilariae then develop into infective larvae. Adult female worms are about 40 to 60 cm length and males 3 to 6 cm in length. These worms can live up to 18 years.

Clinical Features

- In onchocerciasis, tissue damage occurs due to microfilariae and not due to adult worms.
- In the skin, pruritus and papular rash are the most frequent manifestations. Subcutaneous nodules form around the adult worms and are seen commonly over bony prominences. Chronic inflammatory changes in skin result in loss of elasticity, atrophy, fibrosis and premature wrinkling.
- In the eye, the most common early finding is conjunctivitis with photophobia. Corneal inflammation (keratitis) occurs due to microfilaria which leads to neovascularization, corneal scarring and formation of opacities. This leads to blindness. Inflammation in the anterior and posterior chambers frequently results in anterior uveitis, chorioretinitis, and optic atrophy.
- Lymphadenopathy is usually present.

Diagnosis

- Diagnosis can be confirmed by the detection of an adult worm in an excised nodule or microfilariae in a skin snip.

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- Ultrasound can also visualize worm in the subcutaneous nodules.
- Eosinophilis and serum IgE levels are elevated.
- Antibody detection:
  - Ov16 card test: Antibodies against this antigen have been shown to yield high sensitivity (approximately 80%) and specificity (approximately 85%).
  - An ELISA-based test using a cocktail of 3 antigens (Ov7, Ov11, Ov16) has also been used to detect antibodies. It has 97% sensitivity and 100% specificity.
- PCR to detect onchocercal DNA in skin snips are highly sensitive and specific but not available everywhere.
- *Diethylcarbamazine (DEC) patch test (mazzotti reaction)*: Topical application of DEC in a cream base (DEC patch) elicits localized cutaneous reactions (pruritus, maculopapular eruptions, dermal edema) in response to dying microfilariae which is highly suggestive of onchocerciasis.

Treatment

- Ivermectin is the drug of choice for onchocerciasis. Repeated dosing at intervals of 3–12 months is recommended for at least 10–12 years.
- Ivermectin is contraindicated in pregnant or breastfeeding women.
- Moxidectin is an antiparasitic drug that is currently being studied by the WHO for use in onchocerciasis. Moxidectin is closely related to ivermectin, but animal studies suggest it might cause more sustained reduction in microfilarial levels.
- Subcutaneous nodules near the head should be excised (because the adult worms are nearer to the eye).

Prevention

- Vector control.
- Community-based administration of ivermectin every 6 to 12 months to interrupt transmission.

Q. Dracunculiasis (guinea worm infection).

Etiology

- Dracunculiasis is a parasitic infection caused by dracunculus medinensis.
- Its incidence has declined dramatically due to global eradication efforts. But cases still occur in Sudan.

Life Cycle

- Humans are the definitive hosts and cyclops (a crustacean) are intermediates hosts. Female dracunculus worm is very thin but length is up to 1 meter.
- Humans acquire infection from ingestion of water containing infective larvae. Larvae penetrate the stomach or intestinal wall, mate, and mature. The adult male worm dies, but female worm develops and migrates to subcutaneous tissues, usually in lower limb.
- A blister forms in the skin and breaks down to form an ulcer through which the worm can come out and release motile, rhabditiform larvae into water. These rhabditiform larvae are ingested by cyclops where they develop into infective larvae. Cyclops release the infective larvae into the water thus completing the cycle.

Clinical Features

- Guinea worm infection is usally asymptomatic. But just before blister formation, there is fever and allergic symptoms like periorbital edema, wheezing, and urticaria. The emergence of the worm is associated with local pain and swelling. Sometimes the worm is visible to the naked eye when it comes out. Fever and local symptoms subside when the blister ruptures releasing larva-rich fluid. The ulcer slowly heals but can become secondarily infected. Occasionally, the adult worm does not emerge but becomes encapsulated and calcified.

Treatment

- Emerging adult worm can be gradually extracted by winding a few centimeters on a stick every day. Worms may be excised surgically. Niridazole can be used but not very effective. Guineaworm infestation can be prevented by the provision of safe drinking water.

Q. Describe the etiology, life cycle, clinical features, investigations and management of schistosomiasis (bilharziasis).

Etiology

- Schistosomiasis is also known as bilharziasis after Theodor Bilharz who first identified the parasite. It is caused by infection with parasitic blood flukes known as schistosomes. Schistosomes are trematodes (flat worms) which belong to the phylum platyhelminthes.
- Human schistosomiasis is caused by five species. The intestinal species *Schistosoma mansoni, S. japonicum, S. mekongi, S. intercalatum* and the urinary species *S. haematobium.*

Epidemiology

- These five species are found in South America, the Caribbean, Africa, the Middle East, and Southeast Asia. People between 15 and 20-year age group are affected commonly. It is less common in older age groups probably due to less water exposure.

Life Cycle

- Human infection is initiated by penetration of intact skin with infective cercariae which are released from infected freshwater snails. These cercariae are ~2 mm in length and after penetration reach subcutaneous tissue.
- In the subcutaneous tissue they transform into schistosomula. Schistosomulae reach the lungs and then liver through venous or lymphatic vessels.
- In the liver they mature and sexually mature worms descend into the venous system of specific organs: intestine (*S. mansoni, S. japonicum, S. mekongi,* and *S. intercalatum*) and urinary bladder (*S. haematobium*). Adult schistosome worms measure ~1 to 2 cm in length. In these organs worms mate, and gravid females travel against venous flow to small tributaries, where they deposit their ova.
- Ova can penetrate the venous wall by enzyme secretion and reach the lumen of the intestine or urinary bladder from where they are passed with stools or urine. Some ova are carried by venous blood flow to the liver and other organs.
- Schistosome ova that reach freshwater hatch, releasing free-living miracidia that seek the snail (intermediate host) and undergo asexual multiplication cycles.
- Finally, infective cercariae are shed from snails.

Pathogenesis

- The clinical manifestations seen in schistosomiasis are due to inflammatory reaction to eggs in the tissues. Chronic inflammation leads to granuloma formation and irreversible fibrosis.

Clinical Features

- Most people with intestinal schistosomiasis are asymptomatic. In contrast, most people with urinary schistosomiasis are symptomatic.
- In general, disease manifestations of schistosomiasis occur in three stages.
- During the phase of cercarial invasion, a form of dermatitis called swimmers' itch may be seen. It is seen 2 or 3 days after invasion as an itchy maculopapular rash.
- Acute schistosomiasis is seen during worm maturation, characterized by katayama fever—a serum sickness—like syndrome with fever, generalized lymphadenopathy, hepatosplenomegaly and increased eosinophil counts.
- The clinical manifestations of chronic schistosomiasis are species-dependent. Egg deposition in the intestinal wall (*S. mansoni, S. japonicum, S. mekongi,* and *S. intercalatum*) causes colicky abdominal pain and bloody diarrhea. Eggs can penetrate the bowel adjacent to mesenteric vessels where adult worms are residing. Unshed eggs, which are swept back to the portal circulation and induce granulomatous reactions in the portal tracts. Presinusoidal blockage of blood flow leads to portal hypertension, esophageal varices, and splenomegaly. Right and left upper-quadrant "dragging" pain may be experienced due to hepatomegaly and splenomegaly respectively. Bleeding from esophageal varices may cause hematemesis and malena and may be the first manifestation of the disease. In late-stage disease, cirrhosis and liver failure may develop.
- Deposition of eggs in the urinary blader (*S. haematobium*) causes inflammation and granuloma formation in the urinary bladder leading to dysuria, increased frequency, and hematuria. Obstruction of the lower end of the ureters results in hydroureter and hydronephrosis. Bladder granulomas undergo fibrosis and result in typical sandy patches visible on cystoscopy. Squamous cell carcinoma has been observed to develop in damaged bladder; hence, *S. haematobium* has now been classified as a human carcinogen.
- Lungs can also get affected in schistosomiasis. Embolized eggs lodge in small lung arterioles, and produce acute necrotizing arteriolitis and granuloma formation. Later, fibrosis leads to endarteritis obliterans, pulmonary hypertension, and cor pulmonale.
- CNS schistosomiasis occurs when migratory worms deposit eggs in the brain, induce a granulomatous response and fibrosis. Patients may present with epilepsy. Transverse myelitis may also be seen due to eggs traveling to the venous plexus around the spinal cord. Patients with transverse myelitis present with lower-leg weakness accompanied by bladder dysfunction.

Diagnosis

- H/o travel to endemic areas and exposure to freshwater bodies is central to diagnosis.
- High blood eosinophil count and presence of schistosomal antibodies is highly suggestive of infection. Schistosomal antibodies can be detected by indirect fluorescent antibody test and ELISA.
- Examination of stool or urine may show eggs of schistosoma.
- Plain X-ray of the abdomen or CT scan may reveal intramural calcification in the wall of the bladder or colon.
- Schistosome infection can also be diagnosed by examination of tissue samples, usually rectal biopsies and rarely liver biopsy.

Treatment

- Infections with all major *schistosoma* species can be treated with *praziquantel*. Steroids can be given along with praziquantel to suppress inflammation.

Prevention and Control

- Travelers should avoid freshwater contact especially in endemic areas.
- Application of molluscicides, provision of safe water and disposal of sewage, chemotherapy, and health education are all effective in reducing the prevalence of schistosomiasis.

Q. List the important fungi affecting human beings.

- Fungi are universally present in nature but only a few fungi belonging to Eumycetes group are pathogenic to man.
- The eumycetes group can be divided into:
  1. *Moulds (filamentous, mycelial fungi)*, e.g. the ring-worm fungi, actinomycetes.
  2. *Yeasts (unicellular fungi)*, e.g. *Cryptococcus neoformans.*
  3. Yeast-like fungi, e.g. *Candida albicans.*
  4. Dimorphic fungi, e.g. *Histoplasma capsulatum, Blastomyces dermatitidis, Sporothrix schenckii.*

Q. Describe the etiology, clinical features, diagnosis and treatment of candidiasis.

Etiology

- Candidiasis is a fungal infection caused by yeasts that belong to the genus *Candida.* Out of many species of Candida, *Candida albicans* is the most common yeast causing human disease.
- *Candida albicans* is a normal oropharyngeal and gastro-intestinal commensal.
- Candida species reproduce asexually by budding.

Clinical Features

- *Oropharyngeal candidiasis (thrush)* is common in neonates, patients with diabetes mellitus, HIV infection, dentures, patients treated with antibiotics, chemotherapy, or radiation therapy, patients with xerostomia and those treated with inhaled corticosteroids. Oral candidiasis (thrush) presents as well defined, painless adherent white patches in the mouth, tongue and pharyngeal mucosa. HIV infection should be ruled out in unexplained oropharyngeal candidiasis.
- *Cutaneous candidiasis* usually occurs in macerated skin, such as diapered area of infants, under pendulous breasts. It presents as red macerated areas, paronychia, balanitis, or pruritus ani. Partial alopecia can occur in scalp infections.
- *Vulvovaginal candidiasis* is especially common in the third trimester of pregnancy. It causes pruritus, white discharge, and sometimes pain on intercourse.
- Esophageal candidiasis can cause substernal pain or dysphagia. Most lesions occur in the distal third of the esophagus.
- *Systemic candidiasis* and septic shock can occur especially in immunocompromised persons. It can invade almost any organ. Hematogenous seeding is particularly common in the retina, kidney, spleen, and liver. Kidney involvement causes cystitis, pyelitis, or papillary necrosis. Retinal infection appears as unilateral or bilateral small white retinal exudates. The vitreous humor becomes cloudy, and the patient notices blurring, ocular pain, or a scotoma. Retinal detachment can occur. Infection of liver and spleen can occur in patients with acute leukemia recovering from profound neutropenia. Candida pneumonia is very rare. Candida endocarditis can occur in previously damaged or prosthetic heart valves. The source is often an intravascular catheter or illicit drug injection. Other manifestations include arthritis, subacute peritonitis, brain abscess and chronic meningitis.

Diagnosis

- Pseudohyphae are seen on a wet KOH smear prepared from the scrapings of leison. Diagnosis can be confirmed by culture.
- Since Candida is a normal commensal, positive cultures of urine, sputum, abdominal drains, endotracheal aspirates, or the vagina is not diagnostic.
- Blood cultures are useful in the diagnosis of Candida endocarditis. Serologic tests for antibody or antigen are not useful.

Treatment

- For cutaneous candidiasis, topical antifungals are effective. Nystatin powder or ciclopirox cream or an azole is useful. Clotrimazole, miconazole, econazole, and tolnafate are available as creams or lotions.
- For vulvovaginal candidiasis, azoles are better than nystatin preparations. All azoles are equally efficacious. A single dose of 150-mg fluconazole is more convenient to use for vulvovaginitis than topical treatment but is contraindicated in pregnancy.
- For oral candidiasis clotrimazole troches, can be used five times a day. Oral fluconazole (150 mg daily) can also be used.
- For esophageal candidiasis, oral fluconazole (150 mg once daily for 2–3 weeks) is the treatment of choice. Itraconazole is an alternative. For azole-resistant oropharyngeal or esophageal candidiasis a 2-week course of intravenous amphotericin B (0.3 to 0.5 mg/kg daily) or caspofungin (70 mg for one dose, then 50 mg daily) is effective.

- For invasive candidiasis, intravenous amphotericin B is the drug of choice. Candida endocarditis requires valve replacement along with long-term fluconazole administration.

Q. Describe the etiology, clinical features, diagnosis and treatment of Aspergillosis.

- The term "aspergillosis" refers to illness due to allergy, colonization, or tissue invasion by species of Aspergillus.
- Aspergillus species are *A. fumigatus* (most common), *A. flavus, A. niger, A. nidulans, A. terreus*, and many other species.
- Aspergillus is a mold with septate branching hyphae. Aspergillus is ubiquitous in the environment, and is present on dead leaves, stored grain, compost piles, hay, and other decaying vegetation.
- Infection is seen most often in immunocompromised and diabetic persons. Aspergillus can colonize the damaged bronchial tree, pulmonary cysts, or cavities. Balls of hyphae within cysts or cavities (aspergillomas) may form and can reach several centimeters in diameter.

Clinical Manifestations

- Allergic bronchopulmonary aspergillosis (ABPA) can occur in patients with asthma and cystic fibrosis and lead to worsening of wheezing and breathlessness.
- Invasive aspergillosis pneumonia can occur in immunosuppressed individuals and is difficult to treat. Aspergillus may invade immunosuppressed patients through the skin at a site of minor trauma or through the upper airway mucosa. Rapid extension into the adjacent paranasal sinus, orbit, or face is common. Patients usually have a history of chronic allergic rhinitis, and present with painless proptosis, nasal obstruction, or dull aching pain. CT or MRI scan shows a solid mass pushing out the lateral wall of the ethmoid sinus or the medial wall of the maxillary sinus.
- Aspergillus can grow on cerumen and detritus within the external auditory canal and is called otomycosis.
- Other manifestations include aspergillus keratitis, endophthalmitis, and infection of intracardiac or intravascular prostheses.

Diagnosis

- Detection of hyphae in clinical specimens suggests infection.
- Fungus ball in the lung is detectable by chest X-ray.
- IgG antibody to Aspergillus antigens is found in many colonized patients and almost all patients with fungus ball. Serum IgE antibody is raised in allergic bronchopulmonary aspergillosis.
- Biopsy is required for the diagnosis of invasive aspergillosis of the lungs, nose, and paranasal sinuses, etc.
- Blood cultures rarely yield positive results.

Treatment

- Fungus ball of the lung usually requires lobectomy.
- Allergic bronchopulmonary aspergillosis responds to short courses of steroids.
- Invasive aspergillosis is treated with voriconazole, or itraconazole or liposomal or conventional amphotericin B.

Q. Mucormycosis: Zygomycosis.

Q. Rhinocerebral mucormycosis.

- Mucormycosis (zygomycosis, phycomycosis) refers to opportunistic infections caused by members of the genera *Rhizopus, Mucor, Absidia*, and *Cunninghamella*.
- Predisposing factors are:
  - Diabetic ketoacidosis
  - Chronic renal failure
  - Desferoxamine therapy
  - AIDS
  - Corticosteroids or cytotoxic drugs
- Infection commonly involves sinuses, orbits, and the lungs. Disseminated infection can occur in immunocompromised and those receiving chemotherapy.

Clinical Features

- The most common clinical presentation of mucormycosis is rhinocerebral infection. Here the infection involves the nose, pranasal sinuses and then spreads to orbit and adjacent brain. It should be suspected in patients with black necrotic lesions of the nose or sinuses with cranial nerve palsies. Prognosisis is poor in rhinocerebral mucormycosis.

Diagnosis

- Diagnosis is by demonstrating characteristic fungal hyphae in secretions and biopsy specimens. Cultures are frequently negative.

Treatment

- Treatment is by high-dose amphotericin B (1–1.5 mg/kg/d intravenously) or a lipid preparation of amphotericin B for prolonged periods. Posaconazole is also effective. Control of diabetes and other underlying conditions is important. Extensive surgical removal of necrotic involved tissue is essential for cure.

Q. Sporotrichosis

- Sporotrichosis is a chronic fungal infection caused by *Sporothrix schenckii.*
- It is seen worldwide but most cases occur in America and Japan. It is found in soil, sphagnum moss, and decaying wood.
- Infection takes place when the organism is inoculated into the skin—usually on the hand, arm, or foot, especially during gardening. Pulmonary infection develops after inhalation. Invasive infection can occur in immunocompromised persons.
- Lymphocutaneous sporotrichosis is the commonest form seen. A nodule develops at the site of inoculation. This later becomes adherent to the overlying skin and ulcerates. Within a few days to weeks, similar nodules develop along the lymphatics draining this area, and these may ulcerate as well. The lymphatic vessels become indurated and are easily palpable.
- Diagnosis is by culture of the organism. Detection of antibody is useful for diagnosis of disseminated disease, especially meningitis.
- Treatment for localized disease is by itraconazole, 200–400 mg orally daily for several months. Terbinafine, 500 mg twice daily, is also effective. Systemic infection is treated by intravenous amphotericin B.
- Prognosis is good in lymphocutaneous sporotrichosis, and bad in systemic disease.

2 Diseases of Respiratory System

Q. Lung defense mechanisms.

- There are many defense mechanisms in the respiratory tract which protect us from foreign bodies and infections. Pulmonary disease often results from a failure of many of these defense mechanisms. These can be divided into physical and physiological mechanisms and humoral and cellular mechanisms.

Nasal Hair and Mucosal Secretions

- Over 90% of particles greater than 10 microns are trapped by the mucus and hair in the nose.

Humidification

- It happens in the nose and upper respiratory tract. It prevents dehydration of the epithelium.

Coughing, Sneezing or Gagging

- These physiological mechanisms expel any particles or foreign bodies that are inhaled.

Mucociliary Layer of Respiratory Tract

- The epithelium of respiratory tract is covered by a layer of mucus secreted by goblet cells and mucous glands. The respiratory epithelium is also covered by cilia which are in contact with the under surface of the mucus layer. Smaller particles get trapped in this mucus blanket. The cilia push the mucus blanket upwards along with the trapped particles. Cigarette smoking reduces ciliary action. In the *'immotile cilia'* syndrome and *cystic fibrosis* there is reduced ciliary function, leading to stagnation of secretions and recurrent infections.
- *Alpha 1 antitrypsin* is present in lung secretions. It inhibits chymotrypsin and trypsin and neutralizes proteases and elastase which cause damage to lung tissue.
- *Antioxidant defences* include enzymes such as superoxide dismutase and low-molecular-weight antioxidant molecules (ascorbate, urate) in the epithelial lining fluid. They protect against oxidative stress induced damage.

Cellular Defences

- ***Pulmonary alveolar macrophages***: They phagocytose foreign particles and bacteria which reach the alveoli.
- ***Lymphoid tissue***: The lung contains large numbers of lymphocytes which are scattered throughout the airways. These lymphocytes contribute to local immunity through differentiation into IgA-secreting plasma cells.

Intracellular Defenses

- *Lysozyme* is an enzyme found in granulocytes that has bactericidal properties.
- *Lactoferin* is synthesized from epithelial cells and neutrophil granulocytes and has bactericidal properties.
- *Interferon* is produced by most cells in response to viral infection. It is a potent modulator of lymphocyte function. It renders other cells resistant to infection by any other virus.
- *Defensins* are bactericidal peptides present in the azurophil granules of neutrophils.

Q. Pulmonary function tests.

Q. Vital capacity (VC).

Q. Peak expiratory flow rate (PEFR) and its uses.

- Pulmonary function tests are used to measure airflow rates, lung volumes, and gaseous exchange across the alveolar-capillary membrane.
- Many test results depend on the effort of patient, and suboptimal effort is a common cause of misinterpretation of results. All pulmonary function tests are measured against predicted values derived from large studies of healthy subjects. These predictions depend on age, sex, height and weight of the patient.

Indications for Pulmonary Function Testing

- Assessment of the type and severity of lung dysfunction
- Diagnosis of causes of dyspnea and cough

- Monitoring lung function in certain occupations at high risk of lung damage (e.g. mine workers).
- Monitoring response to treatment
- Preoperative assessment
- Disability evaluation.

Contraindications to Pulmonary Function Testing

- Acute severe asthma
- Respiratory distress
- Angina
- Pneumothorax
- Hemoptysis
- Active tuberculosis

Spirometry

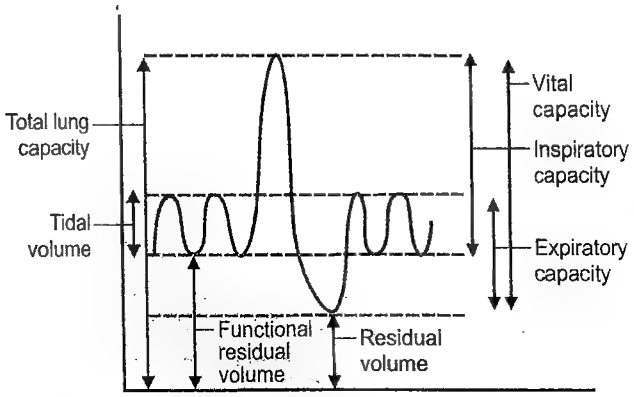

Fig. 2.1: Lung volumes

- Spirometry is measurement of lung volumes and airflow rates by an instrument called spirometer.
- The volume of gas in the lungs is divided into volumes and capacities. Tidal volume (VT) is the amount of gas inhaled and exhaled during a normal breath. Residual volume (RV) is the amount of gas remaining in the lungs at the end of a maximal exhalation. Vital capacity (VC) is the total amount of gas that can be exhaled following a maximal inhalation. FVC is maximal volume of air exhaled with maximally forced effort after maximal inspiration, i.e. vital capacity performed with a maximally forced expiratory effort. The vital capacity and the residual volume together constitute the total lung capacity (TLC). The functional residual capacity (FRC) is the amount of gas in the lungs at the end of normal expiration.
- FEV_1 (forced expiratory volume in the first second) is the amount of gas exhaled during the first second after inhaling to maximum capacity. Normal FEV_1 is about 80%. The ratio of the FEV_1 to the FVC (often referred to as the FEV_1%) is diminished in patients with obstructive lung diseases such as asthma and COPD.
- All lung volumes can be measured by spirometry except residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC). These are measured by helium dilution and body plethysmography.
- Measurement of lung volumes gives an idea about the presence and severity of obstructive and restrictive pulmonary dysfunction. Obstructive dysfunction is characterized by a fall in the ratio of FEV_1 to FVC. Causes of obstructive dysfunction include asthma, COPD, bronchiectasis, bronchiolitis, and upper airway obstruction. Restrictive dysfunction is characterized a reduction in lung volumes with a normal to increased FEV_1/FVC ratio. Causes include interstitial lung diseases, weak respiratory muscles, pleural disease, and prior lung resection.

Peak Expiratory Flow Rate (PEFR)

- It measures the maximum expiratory flow rate over the first 10 milliseconds during a forced expiration. It is measured by a peak flow meter. The patient takes a deep breath and blows as hard as possible into the instrument. A pointer on the calibrated dial of the instrument moves indicating PEFR. The normal PEFR for men is 450 to 700 L/min and 300 to 500 L/min for women.
- PEFR is reduced in airway narrowing and expiratory muscle weakness. PEF values less than 200 L/min indicate severe airflow obstruction. PEFR monitoring can quantify asthma severity, and provide an objective measurement for monitoring response to therapy in asthma. Predicted values for PEFR vary with age, sex, and height. PEFR shows diurnal variation. It is lowest on first awakening and highest many hours later. PEFR should be measured in the morning before taking bronchodilator and in the afternoon after taking a bronchodilator.

Diffusing Capacity of Lungs for Carbon Monoxide (DLCO)

- This reflects the diffusibility of gas across the alveolar/capillary membrane. It is helpful in evaluation of patients with diffuse infiltrative lung disease or emphysema. DLCO is low in emphysema and interstitial lung diseases, whereas it is normal or high in asthma. DLCO is a useful screening test for patients with AIDS who are suspected to have Pneumocystis pneumonia. A normal DLCO is strong evidence against Pneumocystis pneumonia.

Arterial Blood Gas (ABG)

- ABG measurement is indicated whenever acid-base disturbance, hypoxemia, or hypercapnia is suspected.

Pulse Oximetry

- This is a noninvasive method of monitoring oxygen saturation of blood.

Cardiopulmonary Exercise Stress Te

- This is done in patients with unexplained dyspnea. A bicycle ergometer or treadmill is used. Minute ventilation, expired oxygen and carbon dioxide tension, heart rate, blood pressure, and respiratory rate are monitored.

Q. Enumerate the causes an ential diagnosis of cough.

Q. Discuss the approach to a c ough.

- Cough is a forced expulsive manoeuvre, usually against a closed glottis and which is associated with a characteristic sound. *Cough* clears and protects the airways. It is the most frequent symptom of respiratory disease and is one of the most common cause for which medical consultation is sought.
- Cough is initiated by the irritation of cough receptors which exist in the epithelium of the upper and lower respiratory tracts. Cough receptors also exist in the pericardium, esophagus, diaphragm, and stomach. Impulses from stimulated cough receptors travel through afferent nerves (vagus, glossopharyngeal, trigeminal, or phrenic) and go to a "cough center" in the medulla. The cough center generates efferent signals which travel through vagus, phrenic, and spinal motor nerves to expiratory musculature to produce the cough.
- The explosive quality of a normal cough is lost in patients with respiratory muscle paralysis or vocal cord palsy. Vocal cord palsy gives rise to low-pitched, inefficient 'bovine' cough accompanied by hoarseness.

Causes of Cough

Based on the duration, cough can be classified as:

***Acute cough*:** Present for less than *three weeks.*
- *Causes*: Upper respiratory tract infection (such as common cold, pharyngitis), acute bronchitis, aspiration event, inhalation of noxious chemicals or smoke, pulmonary embolism.

***Subacute cough*:** Lasts *three to eight weeks* (pneumonia)
- *Causes*: Tracheobronchitis, such as in pertussis or postviral tussive syndrome.

***Chronic cough*:** Lasts *more than eight weeks*
- *Causes*: Asthma, COPD, bronchogenic Ca, tuberculosis, bronchiectasis, tropical pulmonary eosinophilia, postnasal drip, gastroesophageal reflux disease, interstitial lung diseases (ILD), pulmonary edema due to cardiac failure, ACE inhibitors.

Table 2.1 Differential diagnosis of

Site of origin	Causes	Clinical features
Pharynx	Post-nasal drip due to sinusitis, rhinitis Pharyngitis	History of rhinitis Sore throat, fever
Larynx	Laryngitis, tumor, whooping cough, croup	H/o hoarseness of voice, painful cough, fever. Stridor may be present in severe laryngitis
Trachea	Tracheitis	Retrosternal pain with cough
Bronchi	Acute bronchitis	Dry or productive cough. Worse in mornings. Wheezing present.
	Asthma	Usually dry, worse at night. Associated wheezing is usually present. Asthma-related cough may be seasonal and may worsen upon exposure to cold, dry air, or certain fumes or fragrances.
	COPD	Most patients are smokers. Sputum is usually scanty and mucoid. Associated wheezing is usually present
	Bronchogenic Ca	Persistent cough often with hemoptysis. Patient is usually a chronic smoker. Weight loss may be present.
Lung parenchyma	Tuberculosis	Productive, often with hemoptysis. Low grade fever may be present along with weight loss.
	Pneumonia	Initially dry, later associated with sputum production
	Bronchiectasis	Sputum is mucopurulent and large quantity. Changes in posture induces sputum production
	Pulmonary edema	Often at night. Pink, frothy sputum may be produced. Signs and symptoms of cardiac failure present.
	Interstitial lung disease	Dry, irritant and distressing cough. Associated exertional dyspnea is usually present initially on exertion and later at rest also.
	GERD	Cough is usually nocturnal. Heartburn may be present
Miscellaneous (extrapulmonary causes)	ACE inhibitors	Dry cough. It follows initiation of ACE inhibitors
	Irritation of the external auditory canal by impacted foreign bodies or cerumen	Dry cough. Ear pain and discharge may be present

2

History

Age and Sex

- Bronchogenic ca and COPD are more common in elderly males. Asthma is more common in females.

Onset

- Cough of sudden onset may be associated with foreign body aspiration, allergic reactions and pulmonary edema due to left ventricular failure. Insidious onset cough occurs in COPD, interstitial lung diseases, chronic lung infections such as TB, etc.

Is the Cough Dry/Productive?

- Significant sputum production suggests primary pulmonary pathology (such as pneumonia, lung abscess, bronchiectasis). Dry cough is more likely to be associated with upper airway infections such as rhinitis, pharyngitis, etc.

Associated Symptoms

- Presence of wheezing along with cough suggests bronchial asthma, acute bronchitis, COPD, eosinophilic pneumonia, tropical pulmonary eosinophilia, etc. Presence of breathlessness can occur in pneumonia, acute exacerbation of asthma and COPD, or significant pleural pathology. Presence of fever usually suggests an infectious etiology for cough.

Diurnal Variation in Cough

- Asthma has early morning cough. Cough due to gastroesophageal reflux may increase after food intake and at night due to recumbent position. Pulmonary edema due to heart failure can cause coughing at night which wakes patients (PND).

Intake of any Medications

- ACE inhibitors can cause cough.

Smoking

- One of the commonest causes of persistent cough is smoking. Smoking also leads to COPD and lung cancer which can present as cough.

Occupation

- Dust/chemical exposure in certain occupations can cause cough. For example, coal mine workers may develop chronic cough.

Investigations

- Acute cough usually does not require any investigations. It should be treated symptomatically (with antitussives for dry cough and expectorants for productive cough). Indications for investigation in acute cough include hemoptysis, prominent systemic illness, suspicion of inhaled foreign body and suspicion of lung cancer. However, chronic chough requires many of the following investigations.

Chest

- It can show any pleural or parenchymal pathology such as effusion, pneumonia, mass lesions, etc.

Sinus I... (X-ray or Sinus CT Scan)

- To rule out sinusitis.

Spiro...

- Spirometry should be performed in all patients with chronic cough. It is helpful in diagnosing cough due to asthma and COPD.

High ... Computed Tomographic (HRCT) Scann... hest

- HRCT scanning may be of useful for diagnosing bronchiectasis, interstitial lung diseases or detailed evaluation of any lung pathology.

Bronc... cation Testing

- Should be done in patients without a clinically obvious etiology for cough.

Bronc...

- Bronchoscopy should be done if inhalation of a foreign body or endobronchial pathology is suspected.

24 Hou... ageal pH Monitoring

- To rule out gastroesophageal reflux disease as a cause of cough.

Treatm... ough

- Treat the underlying cause for cough
- Symptomatic management of cough involves use of cough suppressants (such as codeine, dextromethorphan) for dry cough and expectorants for productive cough. Do not suppress a productive cough.

Compli... of Cough

- Cough syncope, rib fracture, pneumothorax, development of hernias.

Q. De... ubbing. Enumerate the causes and ... sm of clubbing.

- Clubbing is enlargement of soft tissues in the terminal phalanges leading to both transverse and longitudinal

curving of nails. Longitudinal curving of nails leads to loss of angle between the nail and nail bed. Normally this angle is less than 180 degrees. In clubbing it is more than 180 degrees.

Causes of Clubbing

RS

- Pulmonary tuberculosis
- Lung abscess
- Bronchiectasis
- Bronchogenic carcinoma
- Mesothelioma
- Interstitial lung disease
- Empyema thoracis
- Cystic fibrosis

CVS

- Infective endocarditis
- Cyanotic congenital heart diseases
- Atrial myxoma

GIT

- Ulcerative colitis
- Crohn's disease
- Primary biliary cirrhosis
- Hepatocellular carcinoma

Endocrine

- Acromegaly
- Myxedema

Miscellaneous

- Hereditary
- Unilateral clubbing—pancost tumor, subclavian artery aneurysm
- Unidigital clubbing—trauma
- Idiopathic

Grading of Clubbing

- *Grade I*: Softening of nail bed. Fluctuation is present at this stage.
- *Grade II*: Loss of angle between the nail and nail bed.
- *Grade III*: Parrot beak appearance nail or drumstick appearance of the digit.
- *Grade IV*: Swelling of fingers in all dimensions associated with hypertrophic pulmonary osteoarthropathy.

Mechanism of Clubbing

- The exact mechanism is unknown.
- It is believed that chronic hypoxia is the main triggering factor for the development of clubbing. Chronic hypoxia leads to opening of arteriovenous fistulas which increase the blood supply to digits and toes leading to soft tissue hypertrophy.

Q. Define dyspnea. What are the mechanisms of dyspnea?

Q. Enumerate the causes of dyspnea.

Q. Give the differential diagnosis of acute onset dyspnea.

- Dyspnea (or breathlessness) refers to the abnormal and uncomfortable awareness of breathing.
- Dyspnea can be acute or chronic. Acute dyspnea develops over minutes to hours. Chronic dyspnea develops over weeks to months.

Table 2.2 Mechanisms of dyspnea

Mechanisms of dyspnea	Causes
Stimulation of intrapulmonary sensory nerves	• Interstitial inflammation • Pulmonary embolism
Increase in the mechanical load on the respiratory muscles	• Airflow obstruction • Pulmonary fibrosis
Stimulation of chemoreceptors	• Hypoxia • Hypercapnia • Acidosis
Reduction of lung compliance	• Pulmonary edema • Severe kyphoscoliosis • Pleural effusion • Pneumothorax

2

Table 2.3 Causes of dyspnea

	Acute dyspnea	Chronic dyspnea
Cardiovascular	• Acute pulmonary edema • Acute myocardial ischemia • Cardiac tamponade	• Chronic heart failure • IHD
Respiratory	• Acute severe asthma • Acute exacerbation of COPD • Pneumothorax • Pneumonia • Pulmonary embolism • ARDS • Foreign body aspiration • Laryngeal edema (e.g. anaphylaxis)	• COPD • Chronic asthma • Bronchial carcinoma • Interstitial lung disease • Chronic pulmonary thromboembolism • Lymphangitis carcinomatosis • Pleural effusion
Others	• Metabolic acidosis (e.g. diabetic ketoacidosis, lactic acidosis, uraemia, overdose of salicylates, ethylene glycol poisoning) • Psychogenic hyperventilation (anxiety or panic-related)	• Severe anemia • Obesity

Table 2.4 Differential diagnosis of acute dyspnea

Condition	Clinical features	Investigations
Pulmonary edema (due to LVF)	*History*: Chest pain, orthopnea, palpitations. Previous h/o cardiac problems. Expectoration of pink frothy sputum. *Examination*: Central cyanosis, raised JVP, sweating, cool extremities, B/L basal lung crepitations. S3 and S4 may be present.	*Chest X-ray*: Cardiomegaly. Prominent pulmonary vasculature. Pleural effusion may be present.
Acute pulmonary embolism	*History*: Risk factors for DVT present (recent major surgery, immobilization, stroke). Sudden onset pleuritic chest pain, hemoptysis, syncope. *Examination*: Central cyanosis, elevated JVP, hypotension. Signs of DVT in the lower limbs. Breath sounds normal.	*Chest X-ray*: Prominent hilar vessels, oligaemic lung fields, prominent pulmonary artery. ECG may show signs of pulmonary embolism such as, S1Q3T3 pattern and right bundle-branch block. Echo shows dilated pulmonary artery, dilated right ventricle.
Acute severe asthma	*History*: H/o dyspnea associated with wheezing, previous h/o asthma. Response to bronchodilators. *Examination*: Bilateral polyphonic ronchi present over the lungs. Usually no crepitations. Prolonged expiration. Tachycardia, pulsus paradoxus and cyanosis may be present.	*Chest X-ray*: Shows hyperinflation. ECG normal. PEFR reduced.

(*contd.*)

Table 2.4 Differential diagnosis of acute dyspnea (*contd.*)

Condition	Clinical features	Investigations
Acute exacerbation of COPD	*History*: Smoking history present. H/o of similar episodes in the past. H/o wheezing present.	*Chest X-ray*: Hyperinflation, increased bronchovascular markings, signs of emphysema.
	Examination: Cyanosis, signs of COPD such as increased AP diameter of chest, pushed down diaphragm. Signs of CO_2 retention (warm periphery, flapping tremor, bounding pulses).	ECG usually normal, but may show signs of pulmonary HTN.
Pneumonia	*History*: Fever with chills and rigors. Cough with purulent sputum. Pleuritic chest pain in lobar pneumonia.	*Chest X-ray*: Pneumonic shadow. Total leucocyte count high.
	Examination: Signs of consolidation present. Crepitations present. Pleural rub may be present if there is associated pleurisy. Signs of pleural effusion may be present if there is syn-pneumonic effusion.	ECG normal.
Metabolic acidosis	History of diabetes/renal failure present. Oliguria or anuria in renal failure. H/o ingestion of ethylene glycol, methanol, etc which can produce metabolic acidosis.	Chest-ray and ECG normal. ABG shows metabolic acidosis. Ketone bodies present in urine in diabetic ketoacidosis. Urea and creatinine high in renal failure.
	Examination: Smell of acetone in diabetic ketoacidosis. Anemia present in CRF. Pedal edema in renal failure.	
Psychogenic hyperventilation	*History*: Previous similar episodes. H/o stressful event preceding the attack. Common in young women.	All investigations are normal.
	Examination: No cyanosis. CVS and RS normal. Carpopedal spasm present due to hyperventilation induced respiratory alkalosis leading to low calcium.	
Pneumothorax	History: Sudden onset unilateral chest pain. H/o wheezing absent.	*Chest X-ray*: Shows pneumothorax.
	Examination: Signs of pneumothorax present (trachea deviated to opposite side, hyper-resonant percussion note, absent breath sounds)	ECG normal.
Upper airway obstruction (foreign body aspiration, laryngeal edema)	*History*: Stridor present. Hoarseness of voice may be present. Patient may be unable to speak.	Chest X-ray may be normal or may show foreign body if it is radio opaque.
	Examination: Inspiratory sound localized to trachea or larynx. Lungs and heart normal.	Direct laryngoscopy or bronchoscopy may show laryngeal edema or foreign body. ECG normal.

2

Q. Solitary pulmonary nodule (SPN).

- Solitary pulmonary nodule (SPN) or "coin lesion" is a lesion less than 3 cm that is both within and surrounded by pulmonary parenchyma.
- A "nodule" is called a "mass" when the size is more than 3 or 4 cm. SPN is a common clinical problem and is detected incidentally on a chest X-ray or CT scan.
- The differential diagnosis of SPN is broad. The main question that has to be answered is whether it is malignant or benign.

Causes of Solitary Pulmonary Nodule

Benign causes	Malignant causes
• Infectious granulomas (tuberculoma, histoplasmosis, coccidioidomycosis) • Wegener's granuloma • Localised pneumonia • Lung abscess • Pulmonary infarct • Arteriovenous malformation • Hamartoma • Hydatid cyst • Bronchogenic cyst • Rheumatoid nodule • Pulmonary sequestration • Pulmonary haematoma • 'Pseudotumor' (fluid collection in a fissure) • Aspergilloma (usually surrounded by air 'halo')	• Primary lung cancer • Carcinoid tumor • Single metastasis • Lymphoma

Diagnosis

- The main task is to distinguish between malignant and benign nodules. Malignant nodules should be excised, whereas benign nodules may be left behind.
- It is not always possible to distinguish between malignant and benign lesions noninvasively. However, certain clinical and radiological features may help in this aspect.
- Clinical features suggesting more chances of malignancy are:
  - *Advanced age*: More than 50 percent nodules are malignant at the age of 60 or above
  - History of smoking or asbestos exposure
  - Previous h/o of malignancy
- Radiographic features suggestive of malignancy are:
  - *Size*: Larger lesions are more likely to be malignant than smaller lesions.
  - Irregular border
  - *Growth*: Fast growing nodules are likely to be malignant
  - Presence of calcification goes in favour of benign lesion. If the nodule remains same size on repeated imaging, it goes in favor of benign lesion.

Investigations

- Chest X-ray.
- CT-scan chest.
- PET scan can noninvasively distinguish between benign and malignant lesions.
- FNAC or biopsy is the gold standard to confirm or rule out malignancy.

Management

- If the probability of nodule being malignant is high, it should be resected.
- If the probability of nodule being malignant is low, it should be followed with serial CT scan. PET scan or sampling of the nodule may be alternatives for patients who are uncomfortable with a strategy of observation.

Q. Define hemoptysis. Discuss the causes, clinical features, investigations, and management of hemoptysis.

- Hemoptysis is coughing out of blood that originates below the vocal cords.
- Hemoptysis is often a sign of serious disease.
- Non-pulmonary sources of hemorrhage—from the nose or the gastrointestinal tract—should be excluded.
- It is classified as trivial, mild, or massive.
- Massive hemoptysis is defined as coughing out more than 200–600 ml in 24 hours or that which leads to hemodynamic compromise.
- Lungs have two sources of blood supply. The pulmonary arteries which arise from the right ventricle and bronchial arteries which arise from the aorta or intercostal arteries both supply the lungs. The bronchial arterial circulation is a high-pressure circuit. Though it contributes to only 1–2% of total pulmonary blood flow, bronchial circulation is frequently the source of hemoptysis.

Causes of Hemoptysis

Respiratory causes

- Tuberculosis (most common cause worldwide)
- Chronic bronchitis
- Bronchiectasis
- Bronchogenic carcinoma
- Bronchial adenoma
- Aspergilloma
- Pulmonary embolism
- Pneumonia
- Lung abscess
- Arteriovenous malformations

Cardiac causes
- Left ventricular failure
- Mitral stenosis

Hematologic causes
- Thrombocytopenia
- Hemophilia
- DIC

Iatrogenic
- After transbronchial lung biopsies, bronchoscopy, etc.

Miscellaneous
- Endometriosis
- Goodpasture's disease
- Wegener's granulomatosis.

Clinical Features

- Patient gives h/o of blood-streaking of sputum or frank hemoptysis.
- Patient is usually anxious.
- Massive hemoptysis may have signs of hemodynamic compromise such as tachycardia, hypotension and cold peripheries.
- Symptoms and signs of underlying disease causing hemoptysis may be present.

Investigations

- Chest X-ray should be done in all cases and may show underlying pathology.
- Hemoglobin, PCV, complete blood count, including platelet count, renal function tests, urinalysis, and coagulation studies should be done.
- High-resolution CT can diagnose unsuspected bronchiectasis and arteriovenous malformations and can also show central endobronchial lesions in many cases.
- Fiberoptic bronchoscopy can be done if the cause of hemoptysis is not evident from noninvasive tests.

Management

- The cause of hemoptysis needs to be identified and treated.
- Massive hemoptysis is life-threatening. Attention should be given to airway and breathing. Patient should be placed in the lateral decubitus position with the involved lung dependent so that the blood does not enter the other lung.
- Volume expansion by using IV fluids or blood transfusion is required to maintain blood circulation.
- Cough suppressants such as codeine syrup and mild sedation (with benzodiazepines) are helpful.
- Nebulized adrenaline
- Oral tranexamic acid (500 mg tds)
- Uncontrollable hemoptysis needs rigid bronchoscopy and specific intervention. Angiography and embolization of the involved bronchial arteries is another option.
- Lung resection should be considered if the bleeding site is localized and not responding to any of the above measures.

Q. Describe the etiology, clinical features and treatment of acute rhinitis (common cold, acute coryza).

Etiology

- Rhinoviruses, coronaviruses, respiratory syncytial virus (RSV) and other viruses.

Epidemiology

- It is more common in children and incidence decreases with advancing age.
- Common cold is a major cause of absenteeism from school and the workplace. The disease spreads through infected droplets. There is no evidence that, exposure to cold temperatures, fatigue, or sleep deprivation causes increased incidence of common cold.

Transmission

- Common cold viruses can be spread by direct contact and aerosols.

Clinical Features

- The incubation period for most common cold viruses is 24 to 72 hours.
- Sneezing, nasal congestion with rhinorrhea, mild malaise, photophobia and watering of eyes. Secondary infection causes the discharge to turn mucopurulent. Nasal obstruction which usually alternates. Dry cough may be noted due to postnasal discharge.
- Examination shows congested nasal mucosa with secretions.

Treatment

- Treatment is mainly symptomatic. Antihistamines like cetirizine, loratidine, etc can be used to decrease nasal discharge. Topical decongestants may be useful to decrease nasal blockage. Antipyretics can be used for headache and body ache. Vitamin C supplementation may help in decreasing the severity of attack.

Complications

- Sinusitis.
- Lower respiratory tract disease—pneumonia, acute bronchitis.

- Exacerbation of congestive heart failure, COPD, and asthma attacks.
- Otitis media.

Q. Acute bronchitis.

- Acute bronchitis is inflammation of medium-sized airways.
- It usually develops as a complication of an upper respiratory tract infection or as an exacerbation of acute infection in COPD.

Etiology

- It is usually due to viral infections, such as adenovirus, rhinovirus or influenza virus in adults and respiratory syncytial virus or parainfluenza virus in children and the elderly.
- Secondary bacterial infection with *Strep. pneumoniae* and *H. influenzae* can occur.
- Atypical infections with *Mycoplasma pneumonia, Chlamydia pneumonia* and *Chlamydia psittaci* can rarely present as acute bronchitis.

Clinical Features

- Patient c/o fever, malaise and dry cough. There can be scanty mucoid sputum which may later become muco-purulent. Dyspnea with wheezing is usually present.
- Examination shows diffuse B/L rhonchi on auscultation. There may be signs of upper respiratory tract infection.

Investigations

- Chest X-ray is usually normal. Total leucocyte count may be high. Sputum gram stain and culture can give an idea about the infecting organism.

Treatment

- Antibiotics are prescribed if bacterial infection is suspected. Cough syrups give symptomatic relief. Bronchodilators may be needed if there are rhonchi on auscultation.

Q. Describe the etiopathogenesis, types, clinical features, differential diagnosis and treatment of bronchial asthma.

- Asthma is a chronic inflammatory disease of airways characterized by increased responsiveness of the tracheobronchial tree to multiple stimuli.
- It is characterised by episodic airflow obstruction, which is reversible.
- Clinically, asthma presents as episodes of dyspnea, wheezing and cough. In between the episodes the person is usually normal.
- An attack of asthma may last a few minutes or hours or days. When the attack is severe lasting days or weeks, it is known as status asthmaticus.

Incidence and Prevalence

- About 10% of the world's population is affected by asthma. It can occur at any age, but commonly starts before the age of 10 years. In childhood, there is 2:1 male/female preponderance, but the sex ratio equalizes by the age of 30.

Etiology

- Asthma is a heterogeneous disease with both endogenous and environmental factors playing a role. Several risk factors have been implicated.

Risk factors involved in asthma

Endogenous factors	Environmental factors
Genetic predisposition	Indoor and outdoor allergens
Atopy	Diet
Airway hyperresponsiveness	Air pollution
Gender	Occupational sensitizers
Ethnicity (common in Europeans)	Respiratory infections
Obesity	
Early viral infections	

Endogenous Factors

- ***Genetic predisposition***: The familial association of asthma and a high degree of concordance for asthma in identical twins indicate a genetic predisposition to the disease. Many chromosomes and linkages are implicated, in particular chromosomes 5, 13, and 14.
- ***Atopy***: Atopy refers to genetic predisposition to develop an allergic reaction (as allergic rhinitis, asthma, or atopic dermatitis) and produce elevated levels of IgE upon exposure to an environmental antigen. Atopy is the major risk factor for asthma, and nonatopic individuals have a very low risk of developing asthma.
- ***Airway hyperresponsiveness***: Airway hyperresponsiveness is due to chronic inflammation of the airways, which leads to bronchospasm and typical symptoms of wheezing, shortness of breath, and coughing after exposure to allergens, environmental irritants, viruses, cold air, or exercise.
- ***Gender***: Asthma predominantly occurs in boys in childhood, with a male-to-female ratio of 2:1 until puberty. After puberty there is equal incidence.
- ***Ethnicity***: Asthma is more common in industrialized western countries.
- ***Obesity***: Obese individuals seem to be at higher risk of developing asthma.

Environmental Factors

- ***Allergens***: Inhaled allergens are common triggers of asthma symptoms and have also been implicated in allergic sensitization. Exposure to house dust mites in early childhood is a risk factor for allergic sensitization and asthma. Domestic pets, particularly cats, have also been associated with allergic sensitization.
- ***Diet***: The role of dietary factors is controversial. Observational studies have shown that diets low in anti-oxidants such as vitamin C and vitamin A, magnesium, selenium, and omega-3 polyunsaturated fats (fish oil) or high in sodium and omega-6 polyunsaturated are associated with an increased risk of asthma. Vitamin D deficiency may also predispose to the development of asthma.
- ***Air pollution***: Air pollutants such as sulfur dioxide, ozone, and diesel particulates, may trigger asthma symptoms, but the role of different air pollutants in the etiology of the disease is much less certain.
- ***Occupational sensitizers***: Exposure to chemicals such as toluene diisocyanate and trimellitic anhydride, may lead to sensitization independent of atopy. Individuals may also be exposed to allergens in the workplace such as small animal allergens in laboratory workers and fungal amylase in wheat flour in bakers.
- ***Respiratory infections***: Though many vial illnesses (rhinovirus, respiratory syncitial virus) have been known to trigger asthma attack, their role in etiology is uncertain. Many patients with asthma have coexistent sinusitis.

Pathogenesis

- Basically, asthmatics have bronchial hyperresponsiveness compared to normal people. Hence, stimuli that normally produce no clinical response can produce clinical symptoms in asthmatics.
- Bronchial hyperresponsiveness is due to persistent subacute inflammation of the airways. The airways are edematous and infiltrated with eosinophils, neutrophils, and lymphocytes. Glandular hypertrophy and denudation of the epithelium is usually present. The inflammatory cells present in airways release mediators on provocation which produce bronchoconstriction, vascular congestion, edema formation, increased mucus production, and impaired mucociliary transport.
- Provocating factors include allergens like pollen, house-dust, mite, drugs like NSAIDs, exercise, inhalation of cold air, infections of the respiratory tract, air pollution, cigarette smoke, strong scents, perfumes, etc.
- Inhalation of allergens by atopic asthmatic individuals leads to the development of two types of responses. Early response, where bronchoconstriction occurs within 10–15 minutes of exposure to an allergen. This type of response usually subsides in one hour. This response is mediated by mast cells in the lumen of the airways, where they interact with inhaled allergens through surface-bound IgE molecules. Histamine and leucotriens released from mast cells mediate bronchoconstriction. The early response is reversed by bronchodilator therapy and can be prevented by prior treatment with a mast cell stabilizer such as sodium cromoglycate.
- In some individuals, the early response is followed by a later phase of bronchoconstriction which begins 4–6 hours after exposure to the allergen and can persist 8–12 hours or longer. The late reaction responds poorly to bronchodilators, but responds to steroids. This late response is mediated by neutrophils, eosinophils and macrophages. These cells contain large quantities of powerful mediators like leukotrienes, platelet activating factor and eosinophilic major basic protein. All these mediators cause an inflammatory reaction responsible for late-phase asthmatic reaction and airway hyperresponsiveness.

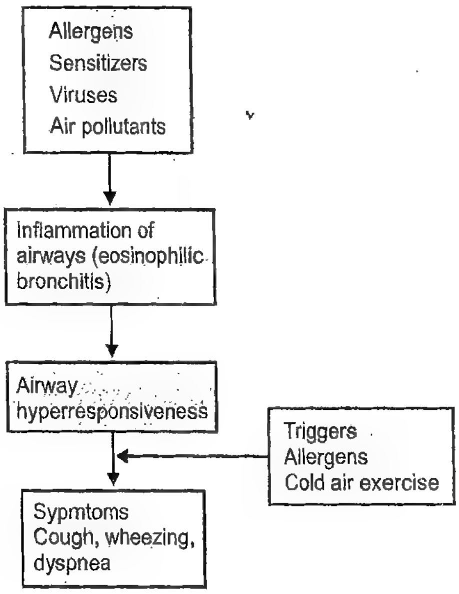

Fig. 2.2: Pathogenesis of asthma

Types

- Asthma can be classified into two types, extrinsic and intrinsic asthma.

Table 2.5 Classification of asthma

	Extrinsic (atopic)	Intrinsic
Etiology	Allergic	Idiopathic
Hereditary predisposition	Yes	No
Onset	Early in life	Late in life
Serum IgE levels	Elevated	Normal
Symptoms	Usually seasonal	Perennial
History of allergy	Yes	No

2

Clinical Features

- The symptoms of asthma consist of a triad of intermittent and reversible attacks of dyspnea, cough, and wheezing. All three symptoms coexist in a typical attack of asthma. Initially patient experiences a sense of constriction in the chest, often with dry cough. Respiration becomes harsh, expiration becomes prolonged and wheezing is heard usually in expiratory phase but can be heard in both phases of respiration.
- Asthma usually worsens at night especially early morning. The end of an attack is usually marked by cough that produces thick, stringy mucus, which often takes the form of casts of the distal airways (Curschmann's spirals). Some patients may just present with intermittent dry cough or exertional dyspnea without any h/o wheezing. In these patients a bronchoprovocation test may be required to make the diagnosis of asthma.
- Examination shows tachypnea, tachycardia, mild systolic hypertension, hyperinflated lungs, with increase in AP diameter of the thorax. High pitched polyphonic rhonchi are heard all over the lungs bilaterally. The presence of cyanosis, severe tachypnoea, pulse rate more than 120 per minute, widened pulse pressure, pulsus paradoxus and completely silent chest on auscultation are indicative of a severe airway obstruction.

Differential Diagnosis

Table 2.6 Differential diagnosis of asthma

Condition	Features
Upper airway diseases • Vocal cord paralysis, vocal cord dysfunction syndrome, laryngeal edema, tracheal narrowing	• Typically present with stridor • Respiratory sound is more over the trachea • Absence of diffuse ronchi over both lung fields • Indirect laryngoscopy or bronchoscopy is diagnostic
Allergic bronchopulmonary aspergillosis (ABPA)	• ABPA occurs in patients with asthma or with cystic fibrosis. • Immediate skin test reactivity to aspergillus antigens • Serum antibodies to *A. fumigatus* positive • Peripheral blood eosinophilia • Lung infiltrates on chest X-ray
Cystic fibrosis	• Onset in childhood • Multisystem involvement • Sweat chloride test diagnostic

(*contd.*)

Table 2.6 Differential diagnosis of asthma (*contd.*)

Condition	Features
Endobronchial disease such as foreign-body aspiration, neoplasm, or bronchial stenosis	• All these conditions usually produce localized rhonchi unlike asthma which produces bilateral diffuse rhonchi.
Acute left ventricular failure (cardiac asthma)	• There is usually S3 and S4. • Bilateral basal lung crepitations may be heard.
Carcinoid tumors	• Usually associated with stridor • Recurrent episodes of bronchospasm can occur
Recurrent pulmonary emboli	• Risk factors for embolism present such as DVT • Pulmonary HTN may be present • Definitive diagnosis requires chest CT or pulmonary angiography
COPD	• Patient is usually a chronic smoker • No true symptom-free periods • History of chronic cough and sputum production present • Progressive worsening of dyspnea
Eosinophilic pneumonias	• Fever and cough present • High eosinophil count in the blood • Chest X-ray shows bilateral diffuse opacities
Systemic vasculitis (Churg-Strauss syndrome)	• Multisystem involvement • Hemoptysis may be present
Psychiatric disorders (conversion reactions and laryngeal spasm)	• Wheezing more on inspiration. Sound localized to trachea. Lung fields clear • Stressors present before the attack • Usually young women

Investigations

- Blood examination may show increased eosinophils.
- Total serum immunoglobulin E levels are frequently elevated.
- *Chest X-ray* may show hyperinflation.
- Pulmonary functions tests show a decrease in the forced vital capacity (FVC), peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV_1). The FEV_1/FVC ratio is usually less than 75%. The diagnosis

of asthma is established by demonstrating reversible airway obstruction. Reversibility is traditionally defined as a ≥15% increase in FEV_1 after two puffs of a β_2-adrenergic agonist. Serial recordings of FEV_1 or peak expiratory flow rate (PEFR) can give an idea about the response to treatment.

- Methacholine/histamine challenge test: Assesses the airway hyperresponsiveness. It is useful when spirometry findings are normal or near normal, especially in patients with intermittent or exercise-induced asthma symptoms. The patient breathes in nebulized methacholine or histamine. Both drugs provoke bronchoconstriction and the level of airflow obstruction is documented by spirometry. However, note that this test is not routinely done in clinical practice.
- Arterial blood gas analysis shows respiratory alkalosis and in severe attacks hypoxia. However, in respiratory failure CO_2 retention causes respiratory acidosis. A rising CO_2 even in the normal range is a bad prognostic sign and indicates impending respiratory failure.
- Skin prick tests are done to identify the allergen in case of allergic or atopic asthma.

Treatment

The goals of asthma treatment are:

- Achieve and maintain control of asthma symptoms
- Maintain normal activity levels, including exercise
- Maintain pulmonary function as close to normal as possible
- Prevent asthma exacerbations
- Avoid adverse effects from asthma medications
- Prevent asthma mortality

Controlling Trigger Factors

- Avoidance of asthma "triggers" is important in successful asthma management. It will prevent frequent attacks and also the requirement of medications. Common asthma triggers include: Allergens, respiratory infections, inhaled irritants such as tobacco smoke and air pollutants, exposure to cold air, emotional stress and gastroesophageal reflux disease. Drugs such as betablockers and NSAIDs can precipitate an attack and should be avoided.

Drug Treatment

- Drugs used in the treatment of asthma can be divided into two categories.
- First category is drugs that relax the smooth-muscle (called "quick relief medications"). Quick relief medicines are used to treat an acute attack. They can be used as and when required basis. These include β-adrenergic agonists, methylxanthines, and anticholinergics.
- Second category is drugs that prevent and/or reverse inflammation (called "long-term control medications"). These medicines prevent or decrease the attacks of asthma. Usually they are used on a regular basis. These include inhaled glucocorticoids, long-acting β_2-agonists, mast cell stabilizers, and leukotriene modifiers.

Table 2.7 Quick relief medications

Drug category	Mechanism of action	Side effects
Adrenergic stimulants Salbutamol, levosalbutamol, terbutaline, adrenaline, salmeterol	They are first line therapy in acute attack. They act through adrenergic β_2 receptors which mediate smooth muscle relaxation. They can be given orally or by inhalation or by nebulization. Adrenaline and terbutaline can be given parenterally also. Salmeterol is long acting and should not be used to treat acute attacks. It is particularly helpful in nocturnal and exercise-induced asthma.	Tremors, tachycardia, and hypokalemia.
Methylxanthines Theophylline, doxofylline	They are considered second-line therapy. They act by inhibiting phosphodiesterase enzyme. They are usually used along with β_2 agonists in acute attacks. However, there is minimal evidence for additional benefit when used with optimal doses of β-agonists.	Nervousness, nausea, vomiting, anorexia, and headache. High levels can cause seizures and cardiac arrhythmias. Doxofyline has less of these side effects.
Anticholinergics Ipratropium bromide, thiotropium bromide	They have only modest efficacy. They are slow to act (60 to 90 min may be required for peak effect). They are particularly helpful in patients with heart disease, in whom the use of methylxanthines and β-adrenergic stimulants may be dangerous.	Blurred vision, urinary retention and cardiac arrhythmias.

2

Long-term Control Medications

- These medicines prevent or decrease the number of attacks by preventing or reversing airway inflammation.

Table 2.8 Long-term control medications

Drug category	Mechanism of action	Side effects
Inhaled glucocorticoids Beclomethasone Budesonide Flunisolide Fluticasone Triamcinolone	Decrease airway inflammation. Since the drug is directly delivered to lungs, they have less systemic side effects and less pituitary adrenal suppression	Oral thrush and dysphonia, cataract formation, decreased growth in children, interference with bone metabolism. Rarely pituitary adrenal suppression
Systemic glucocorticoids Prednisolone Dexamethasone	Decrease in airway inflammation. Especially useful in acute severe attack of asthma but remember that they are not quick relief medications	Pituitary adrenal suppression. May predispose to infections, cataract formation, decreased growth in children, interference with bone metabolism, and purpura
Long acting β_2-agonists Salmeterol Formoterol	Relaxation of bronchial smooth muscle for a long time	Major side effect is tremors, tachycardia, and hypokalemia
Mast cell stabilizers Cromolyn Nedocromil	They inhibit the degranulation of mast cells thus preventing the release of mediators	
Leukotriene modifiers Montelukast Zafirlukast Zileuton	Inhibit the synthesis of leukotrienes which mediate airway inflammation	Zileuton can cause elevations in aminotransferase levels. May predispose to the development of Churg-Strauss syndrome
Anti-IgE antibody Omalizumab	Omalizumab is a blocking antibody that neutralizes circulating IgE and inhibits IgE-mediated reactions. It reduces the number of exacerbations in patients with severe asthma. It should be used when all other medications fail to control asthma. However, it is very expensive and has to be injected subcutaneously	Headache, upper respiratory tract infections, injection site pain, anaphylaxis

Stepwise Treatment of Asthma

Table 2.9 Classification of severity and stepwise treatment of chronic stable asthma

	Daytime symptoms	Night time symptoms	PEFR or FEV_1	Treatment
STEP 1 Mild intermittent	Symptoms ≤2 times a week.	≤2 times a month	≥80%	No daily medication needed. Treat as and when necessary
STEP 2 Mild persistent	Symptoms >2 times a week but <1 time a day	>2 times a month	>80%	Low-dose inhaled glucocorticoids. Alternative treatments are cromolyn, leukotriene modifier, nedocromil, *or* sustained-release theophylline
STEP 3 Moderate persistent	Daily symptoms	>1 time a week	>60% to <80%	Low- to medium-dose inhaled glucocorticoids and long-acting inhaled β_2-agonists. Alternative treatments are cromolyn, leukotriene modifier, nedocromil, *or* sustained-release theophylline
STEP 4 Severe persistent	Continuous symptoms	Frequent	≥60%	High-dose inhaled glucocorticoids *and* long-acting inhaled β_2-agonists *and*, if needed systemic glucocorticoids

Modified from national asthma education and prevention program.

Prognosis

Asthma is a chronic relapsing disorder. Most patients have recurrent attacks but there is no progressive lung damage like COPD.

Q. Acute severe asthma (status asthmaticus).

- Acute episodes of bronchial asthma are one of the most common respiratory emergencies. If not treated in time, death may occur due to asphyxia. Patient should be treated in an intensive care unit.

Clinical Features

- Patient appears severely breathless.
- Patient may be restless or drowsy due to hypoxia and hypercarbia.
- There may be cyanosis, paradoxical pulse, use of accessory muscles, inability to speak in sentences, unable to recline, and marked hyperinflation of the chest.
- A silent chest on auscultation suggests that there is no air movement in and out of lungs due to severe airway obstruction and is a sign of impending respiratory failure.

Investigations

- ECG to rule out MI with pulmonary edema which can also present with dyspnea and wheezing
- Chest X-ray is usually normal except hyperinflation. It is also helpful to rule out other causes of breathlessness such as pulmonary edema, pneumonia, and pneumothorax, etc.
- ABG and PEFR may be done if feasible.

Treatment

Supplemental Oxygen

- Should be given to maintain a SaO_2 >90% or a PaO_2 >60 mmHg. Venturi masks can deliver oxygen better than nasal prongs.

Bronchodilators

- Frequent administration of a short acting β_2-agonist through nebulization is the most important measure. Nebulizations are repeated as necessary till the patient feels better. Inhalers can also be used if the patient can take it. At least three nebulizer treatments should be given in the first hour. Thereafter, the frequency of nebulization can be based on patient response and improvement.
- Administration of anticholinergic bronchodilators such as ipratropium bromide is also helpful.
- IV aminophylline infusion can also be helpful in addition to nebulized bronchodilators.
- Terbutaline injection can be given subcutaneously, and may be repeated 2–4 hourly depending upon the response.

Systemic Corticosteroids

- Corticosteroids should be given by intravenous route.
- Methyl prednisolone should be given at a dose of 40–60 mg every 6 hours for 2 days or until the FEV_1 (or PEFR) returns to 50% of predicted (or 50% of baseline) and then slowly tapered off.
- An equivalent dose of any other steroid (e.g. hydrocortisone 200 mg IV stat and 8th hourly or dexamethasone) can also be used.

Magnesium Sulfate

- Intravenous magnesium sulphate (2 gm infused over 20 min) may be considered in patients not responding to above therapies. It relaxes bronchial smooth muscle by inhibiting calcium influx.

Mechanical Ventilation

- May be required in respiratory failure or impending respiratory failure.

Antibiotics

- Are indicated if there is evidence of infection. Sedatives are contraindicated during an acute attack unless the patient is intubated.

Q. Chronic obstructive pulmonary disease (COPD).

- Chronic obstructive pulmonary disease is a disease state characterized by slowly progressive airflow obstruction that is not fully reversible. COPD includes;
  - *Chronic bronchitis* is a condition characterized by chronic cough, sputum production and airway narrowing.
  - *Emphysema* is a condition characterized by destruction of alveolar walls and enlargement of the alveoli.
  - *Small-airways disease* is a condition in which small bronchioles are narrowed.
- Chronic bronchitis is a clinical diagnosis, whereas emphysema and small-airways disease require biopsy to confirm the diagnosis which is not routinely done.

Epidemiology

- COPD occurs all over the world and is a public health problem. Its incidence is expected to increase further.
- In India, COPD is the commonest lung disorder following pulmonary tuberculosis.

- It affects men more commonly than women probably due to smoking habits. But the prevalence is also increasing in women due to increasing smoking habits among them also.
- There is higher prevalence with increasing age probably due to cumulative lung injury.

Risk Factors

- ***Smoking***: Cigarette smoking is a major risk factor. 95% of cases are smoking-related, typically >20 pack years (1 pack year is 20 cigarettes smoked per day for 1 year). There is less evidence for cigar and pipe smoking probably due to lower dose of inhaled tobacco by-products. Passive (second hand) smoking is also a risk factor for COPD.
- ***Airway hyperresponsiveness***: Patients with increased airway responsiveness are more likely to develop COPD.
- ***Occupational exposures***: Several occupational exposures, like coal mining, gold mining, cotton textile dust etc, are all risk factors for development of COPD. But their effect is less than cigarette smoking.
- ***Air pollution***: Is thought to increase the risk of developing COPD.
- ***Genetic factors***: Also play an important role, e.g. α_1 antitrypsin (α_1AT) deficiency predisposes to the development of COPD.

Pathology

- In COPD, all three components of lungs are affected, i.e. large airways, small airways and lung parenchyma.
- ***Changes in large airways***: Changes in large airways include mucous gland enlargement and goblet cell hyperplasia. The Reid index, which indicates the ratio of thickness of the submucosal glands to that of the bronchial wall, is thus increased. There may be squamous metaplasia of mucous membrane which predisposes to cancer development and also impairs mucociliary clearance. These changes produce chronic cough and sputum production.
- ***Changes in small airways***: Changes in small airways and alveoli include goblet cell metaplasia, loss of surfactant-secreting Clara cells and smooth-muscle hypertrophy. There is chronic inflammation and fibrosis of small airways, characterized by CD8 lymphocyte, macrophage, and neutrophil infiltration, with release of pro-inflammatory cytokines. These changes produce airway obstruction.
- ***Changes in lung parenchyma***: There is destruction of gas-exchanging air spaces, i.e. the respiratory bronchioles, alveolar ducts, and alveoli leading to emphysema. Recurrent infections may perpetuate airway inflammation. These changes are responsible for luminal narrowing, obstruction and impaired gas exchange. Emphysema is classified into 2 pathologic types, centriacinar and panacinar. Centriacinar emphysema is associated with cigarette smoking. It is characterized by enlarged airspaces found (initially) with respiratory bronchioles and often affects upper lobes (remember "C" for ceiling, means above and also for cigarettes). Panacinar emphysema is characterized by enlarged airspaces within and across acinar units. Panacinar emphysema is usually seen in patients with α_1AT deficiency, and often affects lower lobes. Chronic hypoxia in COPD causes thickened pulmonary arteriolar wall and remodeling. This leads to pulmonary hypertension and impaired gas exchange. Pulmonary hypertension can lead to cor pulmonale.

Clinical Features

- Three most common symptoms of COPD are cough, sputum production, and exertional dyspnea. The duration of these symptoms is usually months to years. Onset of these symptoms is gradual. As COPD advances, dyspnea worsens and in the most advanced stages, patients are breathless doing routine activities or even at rest.
- Episodes of exacerbations occur precipitated usually by upper or lower respiratory tract infections.
- Examination may be normal in early stages of COPD. There may be signs of smoking, like odor of smoke, tobacco staining of teeth or nicotine staining of finger-nails. Clubbing is usually not seen in COPD, and if it is present other causes should be searched. Development of lung cancer is the most likely cause of newly developed clubbing in COPD patients.
- Patients with severe COPD may have cyanosis. Accessory muscles of respiration may be active, and patient sits in a characteristic "tripod" position to facilitate the actions of accessory muscles. In patients with severe COPD, expiration is prolonged and there is usually expiratory wheezing. Signs of hyperinflation of lungs are present and include a barrel-shaped chest, pushed down diaphragm, and obliteration of cardiac dullness. Tidal percussion reveals decreased movement of diaphragm as it is already pushed down.
- Patients with predominant emphysema are referred to as "pink puffers," due to lack of cyanosis and pursed-lip breathing. Patients with chronic bronchitis are called "blue bloaters," due to presence of cyanosis and fluid retention. Usually patients have features of both and cannot be simply classified.
- Patients with advanced COPD have wasting and loss of subcutaneous fat. Such wasting is a poor prognostic sign in COPD.

- In advanced COPD patient may develop pulmonary HTN and right heart failure, called cor pulmonale. Such patients present with peripheral edema, raised JVP, congestive hepatomegaly, etc.

Differences between chronic bronchitis and emphysema (Table 2.10)

Investigations

- The hallmark of COPD is airflow obstruction. Pulmonary function testing shows reduction in FEV_1 and FEV_1/FVC. DLCO (diffusibility of carbon monoxide across alveolar membrane) may be reduced in emphysema reflecting destruction of alveolar walls. Arterial blood gas analysis and oximetry may show resting or exertional hypoxemia.
- Hematocrit may be high due to chronic hypoxemia.
- ECG may show evidence of right ventricular hypertrophy.
- Chest X-ray may show bullae, flattening of the diaphragm and hyperlucency in emphysema. On lateral film, large retrosternal air space and localised emphysematous bullae may also be seen in emphysema. Increased broncho-vascular markings may be seen in chronic bronchitis.
- If the patient is less than ≤50 years, with a strong family history, and with a minimal smoking history, serum level of alpha-1 antitrypsin (α_1AT) should be checked.

Treatment

- Only smoking cessation and oxygen therapy have been shown to alter the course of COPD. All other treatments are aimed at improving symptoms and decreasing the frequency of exacerbations.

Smoking Cessation

- All patients with COPD should be strongly urged to quit smoking. Combining pharmacotherapy with traditional supportive approaches increases the chances of smoking cessation. Two drugs, bupropion, and nicotine, are helpful in this regard. Nicotine is available as gum, transdermal patches, inhaler, and nasal spray. All patients should be offered pharmacotherapy, in the absence of any contra-indication to treatment.

Oxygen

- Domiciliary and ambulatory oxygen therapy decreases mortality in patients with COPD. Oxygen can be given during day or at night at home. Using it for 12 hours or more has been shown to provide significant benefit.

Bronchodilators

- These drugs provide symptomatic relief. These include β_2-agonists such as salbutamol, salmeterol, theophylline, ipratopium bromide, etc. Inhaled route is preferred as the incidence of side effects are less. In acute exacerbations these are given through nebulization.

Glucocorticoids

- Inhaled glucocorticoids reduce the frequency of exacerbations. Side effects are oropharyngeal candidiasis and osteoporosis. A trial of inhaled glucocorticoids should be considered in patients with frequent exacerbations, defined as two or more per year. Oral glucocorticoids can be used during exacerbations but long term use of oral glucocorticoids is not recommended because of more side effects than benefits.

Mechanical Ventilatory Support

- This is required in COPD with respiratory failure as happens during exacerbations and advanced stages. Noninvasive positive pressure ventilation (NIPPV) can be given through a tight fitting mask without tracheal intubation. Contraindications to NIPPV include hypotension, altered mental status or inability to cooperate, copious secretions or the inability to clear secretions, craniofacial abnormalities or trauma, extreme obesity, and significant burns in the head and neck region. Invasive mechanical ventilation via an endotracheal tube is indicated for patients in respiratory failure who are not candidates for NIPPV.

Table 2.10 Differences between chronic bronchitis and emphysema

	Chronic bronchitis	Emphysema
Main pathology	Airway inflammation	Destruction of alveolar walls
Main symptom	Cough	Breathlessness
Clinical appearance	Blue bloater	Pink puffer
Sputum production	Copious	Scanty
Cor pulmonale	Common	Only in advanced stage
Respiratory insufficiency	Repeated episodes	Only in advanced stage
Arterial blood gases	Abnormality early in the course of disease	Abnormality only in advanced stage

2

Other Measures

- Intravenous α_1 antitrypsin can be used in patients with deficiency.
- All COPD patients should receive the influenza and pneumococcal vaccine since *H. influenzae* and pneomococcus are the causes of frequent infective exacerbations.
- Lung volume reduction surgery can produce symptomatic and functional improvements in selected patients with emphysema.
- Lung transplantation can be an option for advanced COPD.

Differential Diagnosis

- The most difficult disease to differentiate from COPD is asthma. Asthma typically begins early in life with episodes of dyspnea and wheezing which reverse rapidly and completely.
- Other differential diagnoses include cystic fibrosis, bronchiectasis, eosinophilic granuloma, lymphangioleiomyomatosis and bronchiolitis obliterans.

Prognosis

- COPD is a progressive disease. Poor prognostic factors include weight loss, presence of resting hypoxemia and the need for hospital admission for an exacerbation, especially to intensive care unit.

Q. Define pneumonia. How do you classify pneumonia?

Definition

- Pneumonia is an inflammation of the lung parenchyma due to acute microbial infection, with at least one opacity on chest X-ray.

Classification

Based on the setting in which pneumonia develops:

- Community acquired pneumonia (CAP)
- Hospital acquired (nosocomial) pneumonia
  - Ventilator-associated
  - Non-ventilator-associated

Based on the anatomical distribution of pneumonia:

- Lobar pneumonia
- Bronchopneumonia
- Interstitial pneumonia
- Miliary pneumonia

Q. Discuss the etiology, pathology, clinical features, investigations and management of community acquired pneumonia.

Definition

- Community-acquired pneumonia (CAP) is defined as an acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community.
- Community-acquired pneumonia (CAP) is a common and serious illness with considerable morbidity and mortality.

Etiology

- ***Bacteria*:** *Streptococcus pneumoniae, H. influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae,* Legionella, Gram-negative bacilli, anaerobes, *Mycobacterium tuberculosis, Coxiella burnetii*. Out of these, the first three bacteria (*Streptococcus pneumoniae, H. influenzae, Moraxella catarrhalis*) account for almost 85% of CAP.
- ***Viruses*:** Influenza virus, parainfluenza virus, respiratory syncytial virus.
- ***Fungi*:** Cryptococcus, *Histoplasma capsulatum.*
- Most of the cases are due to bacteria. Nearly 50% of cases of CAP are caused by *Streptococcus pneumoniae* (pneumococcal pneumonia).

Risk Factors for Pneumonia

- Pneumonia is more common in immunocompromised, as occurs in HIV and steroid therapy. Splenectomy is an important risk factor for pneumonia with *S. pneumoniae*.
- Uncontrolled diabetes mellitus is also a risk factor.
- Anatomical defects such as obstructed bronchus, bronchiectasis, or fibrosis lead to recurrent pneumonia.
- Chronic alcoholism predisposes to pneumonia especially aspiration pneumonia.

Pathogenesis

- Microbial agents reach lungs by aspiration, inhalation, hematogenous spread from a distant site, and direct spread from a contiguous site.
- The most common route is microaspiration of oropharyngeal secretions colonized with pathogenic microorganisms. Aspiration can occur postoperatively and also during seizures and strokes. Oropharyngeal secretions contain anaerobic and gram-negative organisms. *H. influenzae* and *S. pneumoniae* can also colonize oropharynx.
- Hematogenous spread occurs in the setting of endocarditis, intravenous catheter infections, or infections at other sites. Staphylococcus usually originates from endocarditis and IV catheter infections, whereas *E. coli* originate from urinary tract infections.
- *Mycobacterium tuberculosis*, fungi, Legionella, *Coxiella burnetii*, and viruses reach the lungs through inhalation of aerosols.

- Once microorganisms reach the alveoli, there is inflammatory response against them. This inflammatory response, rather than the proliferation of microorganisms, triggers the clinical syndrome of pneumonia. The release of inflammatory mediators, such as interleukin (IL)-1 and tumor necrosis factor (TNF), results in fever. Chemokines, such as IL-8 and granulocyte colony-stimulating factor, stimulate the release of neutrophils and attract them to the lung, producing both peripheral leukocytosis and increased purulent secretions. Inflammatory mediators released by macrophages and neutrophils create an alveolar capillary leak. RBCs can also leak into the alveoli causing hemoptysis. The capillary leak results in a radiographic infiltrate and crepitations heard on auscultation. Alveolar filling also results in hypoxemia. Increased respiratory drive leads to respiratory alkalosis.
- All patients with pneumonia have reduced vital capacity, lung compliance, functional residual capacity, and total lung capacity. Decreased compliance, hypoxemia, increased respiratory drive, increased secretions, and occasionally infection-related bronchospasm all lead to dyspnea.
- Pathologically pneumonia manifests as four general anatomical patterns: lobar pneumonia, bronchopneumonia, interstitial pneumonia, and miliary pneumonia.

Lobar Pneumonia

- In lobar pneumonia an entire lobe of lung is involved. Inflammation can involve pleura causing pleuritic chest pain, pleural effusion and pleural rub.
- There are four stages in the course of lobar pneumonia.
- Stage of congestion—occurs during the first 24 h and is characterized grossly by redness and a doughy consistency and microscopically by vascular congestion and alveolar edema.
- The second stage is called red hepatization because of its resemblance to liver in color and consistency. Microscopically this stage is characterized by the presence of erythrocytes, neutrophils, desquamated epithelial cells, and fibrin in the alveolar spaces. Erythrocytes give the appearance of red color.
- The third stage is called gray hepatization because the lung is dry, friable, and gray-brown due to fibrinopurulent exudate, disintegration of red blood cells, and presence of hemosiderin. The second and third stages last for 2 to 3 days each.
- The last stage is stage of resolution, which is characterized by resolution of above changes by enzymatic digestion of exudates, phagocytosis, and coughing out of debris.

Bronchopneumonia

- This pattern of pneumonia involves one or many lobes, and has patchy distribution. It occurs commonly due to aspiration of oropharyngeal secretions and hence usually involves the dependent parts.
- The consolidated areas are poorly demarcated. The neutrophilic exudate is more in bronchi and bronchioles, with centrifugal spread to the adjacent alveoli.

Interstitial Pneumonia

- This pattern of pneumonia involves the interstitium. Inflammation may be patchy or diffuse. There is infiltration of lymphocytes, macrophages, and plasma cells into the alveolar septa. The alveoli may contain a protein-rich hyaline membrane similar to those found in adult respiratory distress syndrome (ARDS).

Miliary Pneumonia

- The pattern is so called because of resemblance of lesions to millet seeds. These lesions are numerous, 2–3 mm in size and diffusely distributed. They result from the spread of the pathogen to the lungs via the bloodstream. The lesions consist of granulomas or foci of necrosis.
- Miliary pneumonia occurs in miliary tuberculosis, histoplasmosis, and coccidioidomycosis. Viruses like herpesvirus, cytomegalovirus, or varicella-zoster virus can cause miliary pattern pneumonia in immunocompromised patients.

Clinical Features

- The onset may be sudden or insidious.
- Fever.
- Cough (with or without sputum).
- Breathlessness.
- Pleuritic type chest pain (in lobar pneumonia).
- There may be other symptoms like headache, nausea, vomiting, diarrhea, myalgia, arthralgia, and fatigue. Confusion may occur in elderly persons.
- General examination shows tachypnea, tachycardia and in severe cases cyanosis.
- RS examination shows dull percussion over the area of consolidation, increased tactile and vocal fremitus, egophony, whispering pectoriloquy, bronchial breath sounds, crepitations and sometimes pleural rub. Crepitations are heard in the stage of congestion and resolution. Bronchial breath sounds are heard in the stage of consolidation in lobar pneumonia. The single most useful sign of the severity of pneumonia is a respiratory rate of >30/min.

Investigations

Imaging Studies

- The most important investigation is chest X-ray. It shows pneumonic patch with or without pleural effusion. However, chest X-ray can be normal in early stages of pneumonia. Hence, it is useful to repeat chest X-ray after 1 or 2 days.
- High-resolution computed tomography (HRCT) can pick up opacities even if chest X-ray is normal.

Sputum Stains and Culture

- Gram's stain can tell whether the infecting organism is Gram positive or negative.
- AFB staining to identify tubercle bacilli.
- Monoclonal antibody staining to identify pneumocystis.
- Special stains for fungi are useful in selected patients.
- Culture and sensitivity can clearly identify the organism and also antibiotic susceptibility. Culture results should always be correlated with those of Gram's staining. If an organism is cultured from sputum which was not seen on Gram's staining, the isolate may be a contaminant from upper airway.
- Some organisms should always be considered as pathogens if isolated from sputum. These include *M. tuberculosis*, Legionella, *H. capsulatum*, and *C. immitis*.

Blood Culture

- Blood should be drawn before starting antibiotics for culture and sensitivity. The organism causing pneumonia is sometimes picked up by blood culture due to bacteremia. Two sets of blood cultures should be drawn.

Serological Tests

- The detection of IgM antibody or a fourfold rise in the titer of antibody to a particular organism is a good evidence for infection by that organism. *Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia psittaci*, Legionella and *Coxiella burnetii*, are often diagnosed serologically.
- Antibody detection is by complement fixation, indirect immunofluorescence, and ELISA.
- Serologic testing is not recommended for routine use.

Polymerase Chain Reaction (PCR)

- Amplification of the DNA or RNA of microorganisms can be used to detect organisms like Legionella spp, *M. pneumoniae*, and *C. pneumoniae* which are not part of normal flora. This test is expensive and is not routinely available.

Detection of Antigens in Urine

- *L. pneumophila* serogroup 1 antigen can be detected in the urine of patients with Legionnaires' disease by ELISA. The urine antigen test is now the most frequently used diagnostic method for Legionnaires' disease. Antigen of *S. pneumoniae* can also be detected in the urine.

Differential Diagnosis

- Pleural effusion
- Pulmonary tuberculosis
- Pulmonary infarction
- Pulmonary oedema
- Pulmonary eosinophilia
- Malignancy
- Alveolitis/cryptogenic pneumonitis/drug-induced pneumonitis
- Systemic necrotising vasculitis
- Interstitial lung diseases.

Treatment of Pneumonia

Admit the patient if any one of the following features is there:

- Respiratory rate >28/min
- Systolic blood pressure <90 mmHg or 30 mmHg below baseline
- New-onset confusion or impaired level of consciousness
- *Hypoxemia*: PO_2 <60 mmHg while breathing room air or oxygen saturation <90%
- Unstable comorbid illness (e.g. decompensated congestive heart failure, uncontrolled diabetes mellitus, alcoholism, immunosuppression)
- Multilobar pneumonia, if hypoxemia is present
- Pleural effusion that is >1 cm on lateral decubitus chest radiography and has the characteristics of a complicated parapneumonic effusion on pleural fluid analysis
- *CURB-65 scoring*: CURB-65 score is used to predict the severity and prognosis of pneumonia. It is very useful to decide whether the patient is to be admitted or not. Each risk factor scores one point, for a maximum score of 5.

	Clinical parameter	Points
C	Confusion	1
U	Urea > or = 20 mg/dl	1
R	Respiratory rate > or = 30 breaths/min	1
B	Systolic BP <90 mm Hg or Diastolic BP < or = 60 mm Hg	1
65	Age > or = 65	1

- If the cumulative score is 0 or 1, the risk of mortality is low and patient can be treated as an outpatient.
- If the score is 2 or 3, the risk is moderate and ideally should be treated as inpatient.
- If the score is 4 or 5, the risk of mortality is high and the patient should be treated as inpatient.

Antibiotic Therapy

- Initially empirical antibiotic therapy is started based on clinical judgment till the organism is identified. Macrolides have excellent activity against *S. pneumoniae* and atypical pathogens like *M. pneumoniae*, *C. pneumoniae,* and Legionella spp and can be used as first line therapy. Doxycycline, also has activity against *S. pneumoniae* and atypical pathogens and can be used for outpatient therapy.
- IV antibiotics can be changed to oral therapy when (1) the white blood cell count is returning toward normal, (2) there are two normal temperature readings (<37.5°C) 16 h apart, and (3) there is improvement in cough and shortness of breath.
- Antibiotics should be given for a minimum of 2 weeks. Azithromycin has a long half life and needs to be given for only 5 days. Patients with severe Legionnaires' disease, pneumonia due to *P. aeruginosa* or other aerobic gram-negative bacilli require 21 days of therapy.
- Patients can be discharged if he is afebrile for 24 h, heart rate is <100/min, respiratory rate is <24/min, systolic blood pressure is >90 mmHg, and oxygen saturation is >90%.

General Measures

- IV fluids
- Oxygen
- Addition of bronchodilators and mucolytics may enhance sputum clearance.
- Physiotherapy to teach effective coughing techniques
- Mechanical ventilation may be required in patients with respiratory failure.

Table 2.11 Initial antibiotic choice for community-acquired pneumonia

Clinical setting	Antibiotic choice
Outpatients Previously healthy and no antibiotics in past 3 months	Macrolide (e.g. clarithromycin 500 mg bd PO × 10 days; or azithromycin 500 mg PO once, then 250 mg/d × 4 days) *OR* Doxycycline 100 mg bid PO × 10 days
Comorbidities or antibiotics in past 3 months	Quinolones, e.g. levofloxacin 500 mg/d PO, or gatifloxacin 400 mg/d PO *OR* A beta-lactam [preferred: high-dose amoxicillin (1 g tid) or amoxicillin/clavulanate (2 g bid); alternatives: ceftriaxone (1–2 g IV qd), cefpodoxime (200 mg PO bid), cefuroxime (500 mg PO bid)] ***plus*** a macrolide or doxycycline
Inpatients, non-ICU	A respiratory fluoroquinolone [moxifloxacin (400 mg PO or IV qd), gemifloxacin (320 mg PO qd), levofloxacin (750 mg PO or IV qd)] A beta-lactam [cefotaxime (1–2 g IV q8h), ceftriaxone (1–2 g IV qd), ampicillin (1–2 g IV q4–6h), ertapenem (1 g IV qd in selected patients)] ***plus*** a macrolide [oral clarithromycin or azithromycin (as listed above for previously healthy patients) or IV azithromycin (1 g once, then 500 mg qd)]
Inpatients, ICU	A beta-lactam [cefotaxime (1–2 g IV q8h), ceftriaxone (2 g IV qd), ampicillin-sulbactam (2 g IV q8h)] ***plus*** Azithromycin or a fluoroquinolone (as listed above for inpatients, non-ICU)
Special concerns If *pseudomonas* is a consideration	An antipneumococcal, antipseudomonal beta-lactam [piperacillin/tazobactam (4.5 g IV q6h), cefepime (1–2 g IV q12h), imipenem (500 mg IV q6h), meropenem (1 g IV q8h)] ***plus*** either ciprofloxacin (400 mg IV q12h) or levofloxacin (750 mg IV qd) *OR* The above beta-lactams ***plus*** an aminoglycoside [amikacin (15 mg/kg qd) or tobramycin (1.7 mg/kg qd) and azithromycin] *OR* The above beta-lactams ***plus*** an aminoglycoside ***plus*** an antipneumococcal fluoroquinolone
If community acquired MRSA is a consideration	Above beta lactams plus add linezolid (600 mg IV q12h) or vancomycin (1 g IV q12h)

Causes of Un-resolving Pneumonia

- ***Wrong diagnosis***: Is it collagen vascular disease, *tuberculosis*, *Pneumocystis*, or another fungus?
- ***Improper antibiotics***: For example, if you are using nafcillin or cloxacillin to treat *Staphylococcus aureus* and your patient is infected with methicillin-resistant *S. aureus*, you should be using vancomycin or linezolid.
- ***Obstructed bronchus***: Due to carcinoma or sequestration of a segment of lung.
- ***Undrained or metastatic pyogenic focus***: For example, empyema, endocarditis, splenic abscess, osteomyelitis.
- Immunosuppressed states.

Causes of Recurrent Pneumonia

- ***Bronchopulmonary disease***: Foreign body, obstruction of bronchus due to enlarged lymph nodes or bronchogenic Ca, COPD, bronchiectasis, lung fibrosis, cystic fibrosis.
- ***Immunodeficiency states***: HIV infection, immunosuppressant drugs, congenital immunoglobulin deficiencies.
- ***Conditions leading to recurrent aspiration***: Gastroesophageal reflux disease, esophageal stricture.

Complications of Pneumonia

- Pleural effusion (common)
- Empyema
- Pneumothorax-particularly with *Staph. aureus*
- Lung abscess
- ARDS
- Sepsis with multiorgan failure
- Ectopic abscess formation (*Staph. aureus*).

Q. Hospital-acquired pneumonia (HAP).

Q. Ventilator associated pneumonia (VAP).

- Hospital-acquired or nosocomial pneumonia refers to a new episode of pneumonia occurring at least 2 days after admission to hospital and not incubating at the time of admission.
- It can be further divided into ventilator associated and non-ventilator associated pneumonia. Ventilator-associated pneumonia (VAP) is pneumonia that develops after 48 hours of mechanical ventilation and not incubating at the time of intubation. Non-ventilator associated pneumonia includes all other types of HAP such as postoperative pneumonia, aspiration pneumonia, etc.
- Both HAP and VAP have similar features and the following description applies to both.

Epidemiology

- 5–20 cases per 1,000 hospital admissions
- Accounts for up to 30% of all nosocomial infections
- Highest rates among intensive care unit (ICU) patients undergoing mechanical ventilation
- About 1.5% of patients develop pneumonia post-operatively.
- HAP lengthens hospital stay by an average of 7–9 days per affected patient.

Risk Factors

Colonization with potential pathogens:
- Decreased gastric acidity due to use of H2 blockers and proton pump inhibitors
- Antimicrobial therapy
- Contaminated ventilator circuits or equipment

Aspiration of oropharyngeal contents into lower respiratory tract:
- Intubation/mechanical ventilation
- Decreased level of consciousness
- Nasogastric intubation
- Reduced cough (general anesthesia, thoracic and abdominal surgery)

Reduced host defenses:
- Corticosteroid treatment, diabetes, malignancy

Bacteremia:
- Infected emboli
- Intravenous cannula infection
- Sepsis

Organisms Causing HAP

- Majority of hospital-acquired infections are caused by gram-negative bacteria. These are Escherichia, Pseudomonas, Klebsiella and Acinetobacter species.
- Other organisms include *Staph. aureus* including MRSA-forms and anaerobic organisms.

Clinical Features

- Fever, leukocytosis, increase in respiratory secretions, and signs of pulmonary consolidation on physical examination, along with a new or changing radiographic infiltrate.
- Other clinical features may include tachypnea, tachycardia, worsening oxygenation, and increased minute ventilation if the patient is on ventilator.

Differential Diagnosis

- Pulmonary edema
- Pulmonary embolism

- Atelectasis
- ARDS
- Pulmonary hemorrhage
- Neoplasm

Laboratory Tests

- Blood cultures
- Sputum culture and Gram staining. Endotracheal aspirate can yield good uncontaminated sample for Gram's stain and culture.
- Chest X-ray shows a new or changing pulmonary infiltrate.
- CT of the chest, if necessary.

Management

- Since organisms causing HAP are likely to be due to multidrug resistant gram-negative bacteria, anti-pseudomonal carbapenems (imipenem/cilastatin and meropenem) are the drugs of choice. Adequate gram-negative coverage should be provided, e.g. a third-generation cephalosporin (e:g. cefotaxime) plus an aminoglycoside (e.g. gentamicin) or meropenem plus flucloxacillin. Colistin appears as effective as other antibiotics for VAP caused by MDR-gram-negative bacilli.
- If MRSA is highly prevalent in the institution and the patient is at risk for MRSA infection, add vancomycin or linezolid.
- Aspiration pneumonia can be treated with co-amoxiclav 1.2 g 8-hourly plus metronidazole 500 mg 8-hourly.
- Physiotherapy for immobile and elderly, and to teach coughing techniques.

Complications

- Increased mortality
- Prolongation of mechanical ventilation
- Pulmonary hemorrhage (especially with Pseudomonas)
- Long-term complications such as bronchiectasis and parenchymal scarring leading to recurrent pneumonias.

Prevention

- Healthcare providers must adhere strictly to hand-washing protocols.
- In patients undergoing mechanical ventilation:
  - *Extubate as early as possible*
  - *Ensure careful periodic drainage of tubing condensate.*
  - *Avoid paralytic agents and heavy sedation that can depress cough*
  - *Continuous suctioning of subglottic secretions*
- Use small-bore enteral feeding tubes:
  - *Place distal to the pylorus*
  - *Avoid large gastric residuals*
- Elevate the head of the bed by >30 degrees.
- Use of kinetic beds

Q. Suppurative or necrotizing pneumonia.

Q. Staphylococcal pneumonia.

Q. Klebsiella pneumonia.

- Suppurative pneumonia is a form of pneumonic consolidation in which there is destruction of the lung parenchyma by the inflammatory process. Suppurative pneumonia can give rise to lung abscess which is a large localised collection of pus. Suppurative pneumonia can occur either as community acquired or hospital acquired pneumonia.
- Organisms responsible—*Staph. aureus* or *Klebsiella pneumoniae.*
- Aspiration of septic material during operations on the nose, mouth or throat under general anesthesia, or of vomitus during anesthesia or coma can produce suppurative pneumonia.
- Bacterial infection of a pulmonary infarct or of a collapsed lobe may also produce a suppurative pneumonia or a lung abscess.

Staphylococcal pneumonia

Clinical Features

- Fever, dyspnea and other constitutional symptoms. Staphylococcal pneumonia is often preceded by influenza.
- Cough with large amounts of foul smelling sputum sometimes blood-stained
- Pleuritic chest pain
- RS examination usually reveals signs of consolidation; signs of cavitation. Pleural rub may be present.
- Dissemination to other organs may cause osteomyelitis, endocarditis or brain abscesses.

Investigations

- Chest X-ray: Homogeneous lobar or segmental opacity. Abscess may be present with an air fluid level. Additional radiographic features include multilobar shadowing. cavitation, and pneumatoceles.
- Sputum Gram stain and culture sensitivity

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Management

- Flucloxacillin 1–2 g 6-hourly IV plus Clarithromycin 500 mg 12-hourly iv If MRSA is suspected, linezolid or vancomycin should be added.

Klebsiella Pneumonia

Clinical Features

- More common in men, alcoholics and diabetics. Upper lobe involvement common. Low platelet count and leucopenia present in many patients.

Treatment

- *Preferred*: Third-generation cephalosporin. For severe infections, add an aminoglycoside.
- *Alternatives*: Aztreonam, imipenem, meropenem, aminoglycoside, or a fluoroquinolone.

Q. Legionnaires disease.

- Legionnaires' disease was first recognized in 1976, when an outbreak of pneumonia took place during the annual convention of the American Legion at a Philadelphia hotel.

Etiology

- The causative agent is *Legionella pneumophila* which is a gram-negative aerobic bacillus. *Legionella pneumophila* causes 2 distinct disease entities; Legionnaires disease (LD) and Pontiac fever. Legionnaires disease (LD) is characterized by pneumonia. Pontiac fever is a short-term illness manifesting as fever and myalgias without pneumonia.
- Its natural habitat is water. It is ubiquitous, and is found in rivers and lakes where it can survive for years at very low temperatures.
- Human infection is acquired through water distribution system colonized by Legionella. Outbreaks have been associated with contaminated water sources, such as shower heads and faucets in patient rooms and air conditioning cooling towers.

Clinical Features

- The incubation period is 2–10 days.
- Males are affected more often. Smokers and the immunocompromised are also more at risk.
- It causes pneumonia which begins with high fever, cough and dyspnea. Extrapulmonary manifestations can occur due to bacteraemia. Gastrointestinal symptoms include nausea, vomiting, diarrhea (watery, not bloody), abdominal pain, and anorexia. Neurologic symptoms include headache, lethargy, encephalopathy, and altered mental status.
- There may be a relative bradycardia.
- Failure to respond to beta-lactam antibiotics is a clue to diagnosis.

Investigations

- Chest X-ray usually shows lobar pneumonia, sometimes with a small pleural effusion.
- Sputum Gram stain shows numerous neutrophils and gram negative rods.
- Hyponatraemia, elevated creatinine and liver enzymes can occur.
- Diagnosis is by the direct fluorescent antibody (DFA) test of the sputum. Serum IgM antibody showing a fourfold rise in titre between paired sera or a single value of >1:256 is also diagnostic.
- *Urinary antigen testing*: Legionella lipopolysaccharide antigen is excreted in the urine and can be detected by ELISA, radioimmunoassay (RIA), or latex agglutination test. The antigen becomes detectable in 80% of patients on days 1–3 of clinical illness. Urine antigen testing is very useful to confirm the diagnosis as this test is not affected by antibiotics and urine sample is easier to obtain than sputum.

Treatment

- Azithromycin or levofloxacin are the antibiotics of choice and are effective as monotherapy.

Q. Discuss the etiology, pathology, clinical features, and management of bronchiectasis.

- Bronchiectasis is an abnormal and permanent dilatation of bronchi.
- It can be congenital or acquired and localized or diffuse.
- It leads to chronic or recurrent infection in the dilated bronchi, copious sputum production and hemoptysis.

Etiopathogenesis

- Development of bronchiectasis is mainly due to two factors; infection and obstruction or both. Infection leads to inflammation and destruction of the bronchial wall, damages respiratory epithelium and impairs mucociliary clearance. This leads to pooling of secretions, and dilatation of bronchi. Dilated bronchi become more susceptible to infection and thus, a vicious cycle results. Pulmonary tuberculosis leads to fibrosis, distorted and dilated bronchi.
- Bronchial obstruction due to any reason can lead to recurrent infections and development of bronchiectasis.
- Some congenital disorders like dyskinetic cilia or mucoviscidosis can also predispose to bronchiectasis.

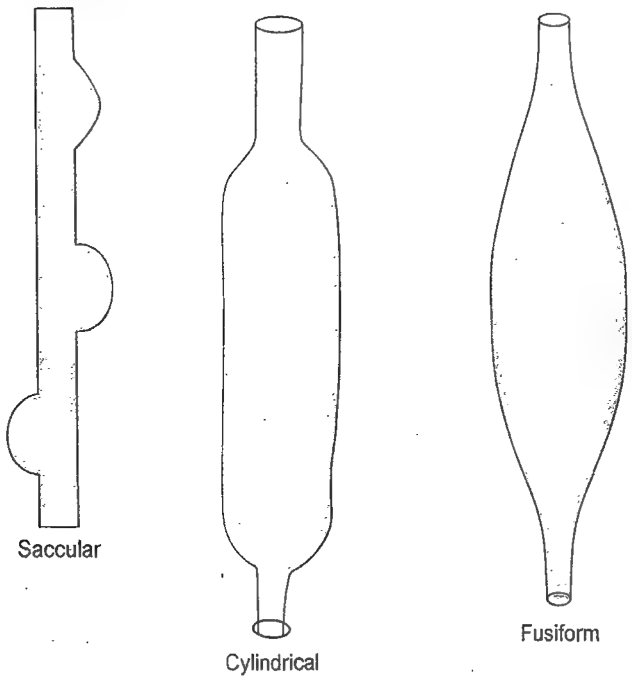

Fig. 2.3: Types of bronchiectasis

- A congenital condition, Kartagener's syndrome is characterized by a combination of situs inversus, bilateral bronchiectasis and abnormal cilia lining the respiratory epithelium. This condition leads to stagnant secretions and repeated bronchial infections which lead to bronchiectasis.
- Bronchiectasis usually affects lower lobe bronchi. Upper lobe bronchiectasis is usually due to tuberculosis.
- Three forms of bronchiectasis have been recognized, namely cylindrical, fusiform, and saccular (cystic).
  - In the cylindrical type, there is uniform dilatation of bronchi.
  - In the fusiform type, dilatation is irregular with tapering at both ends.
  - In saccular type, there are multiple bulgings from side wall of bronchi.
- The bronchial epithelium may be ulcerated with exposure of thin-walled capillaries in the submucosa which are responsible for hemoptysis.

Causes of Bronchiectasis

Bronchial Obstruction

- Foreign body
- Tumor
- Stenosis
- Enlarged lymph nodes
- Impacted secretions

Infections

- Childhood pneumonias in measles, whooping cough
- Pulmonary tuberculosis
- Bronchopulmonary aspergillosis
- Repeated chest infections due to immunodeficient states

Miscellaneous

- Cystic fibrosis
- Kartagener's syndrome
- Alpha-1 antitrypsin deficiency
- Immotile cilia syndrome

Clinical Features

- Persistent or recurrent cough with copious sputum for several years. There is postural variation to cough and sputum quantity depending on which area of the lung is involved. Some patients may have no sputum with cough. This entity is called *bronchiectasis sicca.*
- Sputum is often blood-stained, and occasionally foul-smelling. Hemoptysis can be massive due to erosion of a hypertrophied bronchial artery.
- Patients may have dyspnea and wheezing when underlying COPD is also present.
- When there is secondary infection, quantity of sputum increases, becomes more purulent, foul smelling and often more bloody. Patients may also have fever and other constitutional symptoms.
- Patients are usually malnourished and in a child there may be growth retardation.
- Physical examination may reveal coarse, leathery crepitations, rhonchi, and bronchial breath sounds over the area of bronchiectasis reflecting damaged airways containing secretions and consolidation. Clubbing is usually present. Patients with severe B/L bronchiectasis may have cor-pulmonale and right ventricular failure.

Investigations

- Chest X-ray may show cystic lesions in cystic bronchiectasis. B/L honeycombing (ring shadows) can occur reflecting end on view of dilated bronchi. When seen longitudinally, the dilated and thickened bronchi appear as "tram tracks". Chest X-ray may be normal in patients with limited disease.
- Bronchography is instillation of a radiopaque dye into airways and then taking X-ray images. This can provide excellent visualization of bronchiectatic airways and was once gold standard for the diagnosis of bronchiectasis. But now this technique has been replaced by HRCT.
- High resolution computed tomography (HRCT) of the chest is now the preferred method for diagnosis because it is noninvasive. It can pick up even slight abnormalities missed by chest X-ray.
- Bronchoscopy may be done if a foreign body or adenoma is suspected to be the cause of bronchiectasis.

- In diffuse bilateral bronchiectasis with early age of onset, measurement of sweat chloride levels to rule out cystic fibrosis and assessment of nasal or bronchial cilia or sperm for primary ciliary dyskinesia may be required.
- Pulmonary function tests show both restrictive and obstructive ventilatory dysfunction. Airway obstruction is due to retention of secretions and bronchial inflammation, whereas the restrictive changes are due to atelectasis and scarring of the lung parenchyma.

Complications

- Massive haemoptysis, empyema, respiratory failure, corpulmonale, pericarditis, metastatic abscesses, and secondary amyloidosis.

Management

- Medical management consists of postural drainage of the secretions, expectorants, bronchodilators and antibiotics. Regular physiotherapy prevents accumulation of secretions and repeated infections. Use of mucolytics like N-acetylcysteine and bromhexine may help in clearing the secretions. If secondary infection is suspected, broad spectrum antibiotics such as ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, or cefaclor is given till the organism is identified. If *P. aeruginosa* is suspected, a quinolone or aminoglycoside or third-generation cephalosporin is used. Metronidazole can be added if anaerobic infection is suspected. Bronchodilators relieve airflow obstruction and aid clearance of secretions.
- Surgical resection is considered when bronchiectasis is localized and the morbidity is substantial despite adequate medical therapy.
- Bronchial artery embolisation can be considered in patients with recurrent large hemoptysis.

Q. Etiology, clinical features and management of lung abscess.

- Lung abscess is defined as necrosis of the pulmonary tissue and formation of cavity containing necrotic debris or fluid caused by microbial infection. It is usually single and measures >2 cm in diameter. The formation of multiple small (< 2 cm) abscesses is occasionally referred to as necrotizing pneumonia.
- Lung abscess may be acute or chronic, single or multiple.

Etiology

- Lung abscess is caused most frequently by bacteria, usually anaerobes.
- The routes of infection include inhalation, aspiration, hematogenous, transdiaphragmatic or transthoracic route. Lung abscess can also occur due to secondary infection of a pre-existent cavity, cyst or bulla. A lung neoplasm may cavitate and mimic lung abscess.
- Aspiration of the oropharyngeal secretions and subsequent abscess formation can occur in patients with altered consciousness, anesthesia, alcohol intoxication, sedative drugs, head injury, cerebrovascular accidents, esophageal stricture, and during seizures. Poor oral hygiene and dental caries is a risk factor for development of abscess.
- Bronchial obstruction due to tumor or foreign body and bronchiectasis may predispose to secondary infection and abscess formation. Immunodeficient state is also a predisposing factor.

Organisms Causing Lung Abscess

Aspiration-prone host
Abscess following aspiration has usually a polymicrobial flora containing gram-negative bacilli and anaerobes. Anaerobes such as *Bacterioides fragilis,* Fusobacterium spp. and anaerobic cocci including Peptococcus spp. and microaerophilic streptococci. Common aerobic organisms include *Streptococcus milleri* (member of viridans group), *Streptococcus pyogenes* and *Staphylococcus aureus.* Common gram-negative organisms are *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.*

Immunocompromised host
M. tuberculosis, Nocardia asteroides, Rhondococcus equi, Legionella spp., *P. aeruginosa,* Enterobacteriaceae (especially *Klebsiella pneumoniae*), Aspergillus spp., Cryptococcus spp.

Previously healthy host
Bacteria: S. aureus, S. milleri, K. pneumoniae, group A streptococcus; Gemella, Legionella, and Actinomyces spp.
Parasites: Entamoeba histolytica, Paragonimus westermani, Strongyloides stercoralis.

Pathology

- By definition a lung abscess is more than 2 cm in diameter and has a wall of variable thickness. The abscess cavity is usually filled with purulent secretions.
- Posterior segments of the right upper lobe and apical segments of the lower lobe of both lungs are affected commonly after aspiration. Abscesses due to other mechanisms may involve any segment. An abscess usually communicates with a bronchus.

Clinical Features

- Patients usually present with high-grade fever with chills and rigors. Cough with purulent sputum, dyspnoea and chest pain are usually present. Hemoptysis may also be present.
- Physical examination may show clubbing. There may be amphoric or cavernous bronchial breath sounds over the cavity. Crepitations and pleural rub may be heard.

Investigations

- Blood count shows polymorphonuclear leucocytosis.
- X-ray chest shows the abscess cavity with fluid level.
- CT scan may be required to differentiate lung abscess from loculated empyema.
- Smear and culture of sputum or bronchial aspirate can identify the causative organism.
- Bronchoscopy is indicated if foreign body or tumour is suspected.

Complications

- Bronchopleural fistula and empyema formation
- Pericarditis
- Massive haemoptysis
- Metastatic infection (brain abscess, purulent meningitis)
- Secondary amyloidosis may develop in chronic lung abscess

Treatment

- Intravenous clindamycin or amoxicillin-clavulanate can be used as initial therapy pending organism identification. Penicillin plus metronidazole is another option especially if aspiration is susupected.
- Lung abscess which develops in hospital are usually caused by *Klebsiella pneumoniae, Pseudomonas aeruginosa, S. aureus* and anaerobes, and require treatment with a combination of a third-generation cephalosporin, aminoglycoside and metronidazole.
- Antibiotic therapy should be continued until radiographic resolution of the abscess cavity is demonstrated. Usually 6 to 8 weeks of therapy is required.
- Physiotherapy in the form of postural drainage can help clear the secretions.
- Chronic abscesses not responding to medical therapy require surgical resection.

Q. Empyema.

- Empyema is collection of pus in the pleural space.

Causes of Empyema

Traumatic	Penetrating chest injuries
Iatrogenic	Thoracic surgery Following pleural aspiration, and intercostal tube drainage
Infections	Pneumonia Tuberculosis Bronchiectasis Lung abscess Mediastinitis Osteomyelitis of ribs, vertebrae
Spread from other sites	Rupture of subphrenic abscess and liver abscess

Pathology

- Initially, the pleural fluid is thin, but later it becomes thick due to fibrin deposition.
- Adhesions may form leading to loculations.

Clinical Features

- Patient usually presents with fever, pleuritic chest pain, and dyspnea. Cough with purulent sputum may be seen in bronchopleural fistula.
- Examination reveals decreased chest movement, stony dull percussion note, absent breath sounds, tenderness and bulging of intercostals spaces on the side of empyema. Clubbing is usually present.
- Rarely, empyema can penetrate the pleura and collect in the subcutaneous tissue forming a swelling on the chest wall which increases on coughing (cough impulse). This is called "empyema necessitans", and is seen in actinomycotic infection.
- Patient may be toxic with signs of sepsis. Chronic empyema leads to pleural thickening, chest deformity and scoliosis. Extensive pleural calcification may occur.

Diagnosis

- Empyema should be suspected in any case of pneumonia with pleural effusion.
- Chest X-ray appearance of empyema is the same as that of pleural effusion, but loculations may be present more often.
- Ultrasound of chest can show fibrin strands suggesting empyema.
- Aspiration of pleural fluid can confirm the diagnosis of empyema. Gram stain, AFB stain and culture should be done from the pleural aspirate. The pleural fluid pH is usually less than 7.2, LDH level is more than 1000 IU/L and glucose content is less than 60 mg/dl.

Complications

- Sepsis with septic shock
- Pleural thickening with calcification and fibrosis
- Bronchopleural fistula
- Deformities of the thoracic cage
- Chronic discharging sinus
- Secondary amyloidosis
- Metastatic infection

Management

- Antibiotics are given based on culture and sensitivity. Pending culture sensitivity results, combination of penicillin (gram-positive cover), an aminoglycoside (gram-negative cover) and metronidazole (anaerobic cover) may be used. The duration of treatment is usually six weeks.

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- Empyema due to tuberculosis or other organisms such as *Entamoeba histolytica* and actinomyces should be treated with appropriate antibiotics.
- Empyema should be drained either by closed or open methods. Closed drainage is done by needle aspiration or intercostal tube drainage under a water seal. ICD can be removed when the drainage is less than 25 to 50 ml in 24 hours for two consecutive days. Open drainage by thoracotomy is required if there is bronchopleural fistula or multiple loculations, or the fluid is too thick.

Q. Describe the etiology, pathogenesis, clinical features, diagnosis and management of pulmonary tuberculosis.

Q. Describe the etiology, pathogenesis, clinical features, diagnosis and management of post primary (reactivation) pulmonary tuberculosis.

Q. Antituberculous drugs.

Q. Newer methods of diagnosis of tuberculosis.

Q. Sequelae of tuberculosis.

- Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis.* It is one of the oldest infections known. It usually affects the lungs, although in up to one-third of cases other organs are involved. Tuberculosis is curable if properly treated. Untreated disease can be fatal within 5 years in more than half of cases.

Etiology

- *M. tuberculosis* is a rod-shaped, non-spore-forming, aerobic bacterium. Robert Koch discovered this bacillus.
- They do not take up Gram stain because of the high lipid content, but can be stained by the Ziehl-Neelsen stain. After staining with Z-N stain they resist decolorisation with acid. That is why they are also known as acid-fast bacilli.
- Acid fastness is mainly due to the organism's high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. Other microorganisms which are acid fast are Nocardia, Rhondococcus, *Legionella micdadei,* Isospora and Cryptosporidium.
- Mycobacteria are rapidly destroyed by sunlight and ultraviolet light. But if protected from sunlight they can survive for weeks to months. Tubercle bacilli in milk are killed by pasteurization.

Epidemiology

- According to the WHO, there were 8.8 million incident cases of TB worldwide in 2010. India is the highest TB burden country with an estimated incidence of 2.2 million cases. It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB. Recent data on global trends indicate that incidence is falling in most regions.
- The incidence of tuberculosis is highest during late adolescence and early adulthood due to unknown reasons. The incidence among women peaks at 25 to 34 years of age. The risk increases in the elderly, due to waning immunity and comorbidity.
- Genetic factors also play a role in innate non-immune resistance to infection with *M. tuberculosis.* Hence, susceptibility to tuberculosis differs in different populations.
- Tuberculosis spreads by airborne droplet nuclei produced by patients with active pulmonary tuberculosis. The risk of infection is directly related to the duration and intensity of exposure to air contaminated with infected droplets. Patients whose sputum is smear-positive can have up to 1 lakh organisms per ml of sputum and are highly infectious. Respiratory secretions aerosolized by coughing, sneezing or talking are sufficiently small (1–10 μ) and can remain suspended for long periods. A cough can produce 3000 infectious droplet nuclei. Talking for 5 minutes can also produce similar number droplets, and sneezing produces more droplets. A single droplet is sufficient to infect a person if prolonged exposure is there. In hospital wards, six air changes per hour eliminate infectiousness; hence, good ventilation is important to prevent infection.

Pathogenesis

- Majority of inhaled droplet nuclei are trapped in the upper airways and expelled by ciliated mucosal cells. A small fraction reaches the alveoli. There, alveolar macrophages phagocytose the tubercle bacilli. Now two things can happen. Either macrophages kill the bacilli and clear the infection or the bacilli multiply within macrophages and kill the macrophages.
- If bacilli multiply within macrophages, they produce cytokines and chemokines that attract other phagocytic cells, including monocytes, other alveolar macrophages, and neutrophils, which eventually form a nodular granulomatous structure called the tubercle. Tubercles have central caseative necrosis. These lesions may heal by fibrosis and calcification, or undergo further evolution. If the infection is not controlled, the tubercle enlarges

and the bacilli spread to local lymph nodes. This leads to local lymphadenopathy. The lesion produced by the expansion of the tubercle into the lung parenchyma with local lymphadenopathy is called the Ghon complex.
- The caseous center of the lesion liquefies and breaks into bronchi. Once the lesion empties into bronchi, cavities are formed. Bronchial walls as well as blood vessels are invaded and destroyed, leading to more cavities and hemoptysis. The liquefied caseous material, containing large numbers of bacilli, is brought out as sputum and infectious to others.
- The bacilli continue to multiply until an effective cell-mediated immunity (CMI) develops usually two to six weeks after infection. If effective CMI does not develop, the infection continues to spread and destroy the lung. Bacilli may spread hematogenously to produce disseminated TB. Miliary TB is disseminated disease with lesions resembling millet seeds.
- Even after healing, viable bacilli may remain dormant within macrophages or in the necrotic material for many years or throughout the patient's life. Reactivation TB results when the persistent bacteria in a host begin to multiply due to decrease in host immunity. Immunosuppressive conditions associated with reactivation TB include: HIV infection, diabetes mellitus, corticosteroid use and old age.
- When immunity develops to tubercle bacilli, the person also shows reactivity towards PPD skin test. Hence, PPD skin test positivity suggests *M. tuberculosis* infection. This reactivity is mainly due to previously sensitized CD4+ lymphocytes, which are attracted to the skin-test site.

Risk factors for developing active tuberculosis among persons who have been infected with tubercle bacilli:
- Recent infection (<1 year)
- Fibrotic lesions (spontaneously healed)
- HIV infection
- Silicosis
- Chronic renal failure/hemodialysis
- Diabetes
- IV drug use
- Immunosuppressive treatment
- Gastrectomy
- Tobacco smoking
- Malnutrition

Clinical Features

- Manifestations of pulmonary tuberculosis (TB) can be divided into primary, reactivation (post primary) and endobronchial tuberculosis.

Primary Tuberculosis

- Fever is the most common symptom. It is usually low grade and can last for weeks to months.
- Pleuritic chest pain and pleural effusion can be present. Other symptoms are fatigue, cough, arthralgias and pharyngitis. The physical examination is usually normal but signs of pleural effusion may be present.

Post-primary Disease (Reactivation Tuberculosis or Secondary TB)

- Reactivation TB accounts for most of the adult cases in the non-HIV-infected population. It results from reactivation of a previously dormant focus acquired at the time of the primary infection. It affects apical posterior segments commonly.
- Symptoms begin insidiously and include cough, weight loss and fatigue, fever and night sweats. Patients may present with only fever and night sweats without cough. Pleuritic chest pain, dyspnea and hemoptysis are also reported by some patients. Pleuritic chest pain signifies inflammation abutting or invading the pleura. Dyspnea occurs when there is extensive parenchymal involvement, pleural effusion, or a pneumothorax. Pleural effusion can progress to frank empyema.
- Initially cough may be dry. But as the disease progresses, cough becomes productive with yellow or yellow-green sputum. Frank hemoptysis, due to caseous sloughing or endobronchial erosion, typically is present later in the disease and is rarely massive.
- Physical findings include weight loss, signs of pleural effusion, crepitations and signs of consolidation if large areas are involved. Amphoric breath sounds may be heard over cavities. Clubbing may be present.

Endobronchial Tuberculosis

- Endobronchial tuberculosis may develop by direct extension to the bronchi from an adjacent parenchymal focus such as cavity, or spread of organisms to the bronchi through infected sputum.
- Endobronchial TB can cause obstruction, atelectasis, bronchiectasis, and tracheal or bronchial stenosis.
- Symptoms of endobronchial TB include cough with sputum and hemoptysis
- Physical findings include diminished breath sounds, rhonchi or wheezing due to narrowing of bronchus.

Diagnosis

- ***Chest X-ray:*** In primary tuberculosis it may show pleural effusion, pulmonary infiltrates usually on right side and perihilar region. In post-primary tuberculosis it may show cavities, hilar adenopathy and fibrosis.

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- *Microscopy*: Sputum is stained by Ziehl-Neelsen stain. At least three sputum samples should be tested. Demonstration of acid-fast bacilli on sputum smear does not confirm the diagnosis of tuberculosis, since saprophytic non-tuberculous mycobacteria may colonise the airways or cause pulmonary disease. Cultures of sputum for *M. tuberculosis* is diagnostic. In patients who do not produce sputum or those whose sputum is negative for AFB but still TB is suspected, fiberoptic bronchoscopy can be used to obtain specimens. Through fiberoptic bronchoscopy bronchial washings are obtained and tested for AFB. Fiberoptic bronchoscopy can also diagnose endobronchial TB and biopsies can also be obtained. Early morning aspiration of gastric contents after an overnight fast is an alternative to bronchoscopy. Gastric aspirates are suitable only for culture and not for stained smear, because non-tuberculous mycobacteria may be present in the stomach in the absence of tuberculous infection.
- *Culture*: Tubercle bacilli grow slowly in culture. Hence it may take 6–8 weeks to grow them in solid media. A radiometric culture system (*Bactec*) may allow detection of mycobacterial growth in as little as several days. Once *M. tuberculosis* is grown in culture, drug sensitivity tests also can be done to rule out MDR TB. Sensitivity testing is done when a treatment regimen is failing, and when sputum cultures remain positive even after 3 months of therapy. *M. tuberculosis* may sometimes be cultured in blood of 15% of patients with tuberculosis. Pleural fluid cultures for *M. tuberculosis* are positive only rarely.
- *Histopathology*: In patients with TB pleural effusions, needle biopsy of the pleura reveals granulomas in 50% of patients.
- *Serologic tests*: Demonstration of IgG antibody against mycobacterial antigens by ELISA. This test is not done routinely.
- *Polymerase chain reaction*: To detect DNA of TB bacilli is a useful test but is expensive. It is used to diagnose CNS tuberculosis like TB meningitis.
- *Adenosine deaminase (ADA)*: ADA level of > 50 U/L in pleural fluid is highly suggestive of tuberculous pleural effusion.
- *PPD skin testing (Montoux test)*: In the absence of a history of BCG vaccination, a positive skin test provides additional support for the diagnosis of tuberculosis.

Newer Methods of Diagnosis of Tuberculosis

- *Immunodiagnosis*: Involves the estimation of antibodies or tuberculous antigen or immune complexes in the serum of the individual by radio-immuno assays (RIAs), fluorescent antibody test, and enzyme-linked immunosorbent assay (ELISA). These tests are sensitive but not very specific. Using monoclonal antibodies to detect tuberculous antigen and antibodies is more specific. Monoclonal antibodies can also be used to purify antigens for immunodiagnosis.
- *DNA probes*: *M. tuberculosis* specific DNA probes can be used to detect the presence of complementary DNA or RNA sequence of mycobacterium test samples.
- *Polymerase chain reaction (PCR)*: Here the DNA sequence of MTB if present in a sample is isolated using a probe and amplified until there is enough genetic information to be identified. It can be used to quickly identify *M. tuberculosis*.
- *IFN-gamma release assays (IGRA)*: These assays measure T cell release of IFN-gamma in response to stimulation with TB-specific antigens. A positive test result suggests that *M. tuberculosis* infection is likely; a negative result suggests that infection is unlikely. An indeterminate result indicates an uncertain likelihood of *M. tuberculosis* infection. There are two commercially available kits T-SPOT.TB and QuantiFERON-TB Gold. IGRAs are more specific than tuberculin test because of less cross-reactivity due to BCG vaccination and infection by nontuberculous mycobacteria. IGRA does not help differentiate latent tuberculosis infection from active tuberculosis.

Treatment

- The aim of treatment is not only to cure patients but also to prevent transmission to others. At least three anti-TB drugs should be used to initiate therapy in order to reduce bacterial resistance.

Antituberculous Drugs

- There are five main first-line drugs for the treatment of tuberculosis: Isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin (HRZES). Note that streptomycin is put under first line drugs by WHO; whereas it is put under second line drugs by CDC (centre for disease control).
- Rifampicin, isoniazid, and streptomycin are bactericidal. Pyrazinamide and ethambutol are bacteriostatic.
- The treatment regimen usually consists of initial intensive treatment for 2 months followed by 4–6 months of continuation phase. Initial phase includes 4 or more drugs and continuation phase 2 or more drugs.

Table 2.12 First line drugs

Drug	Mechanism of action	Dose/day	Side effects
Isoniazid	Inhibition of mycolic acid synthesis. It also disrupts DNA, lipid, carbohydrate synthesis and metabolism	5 mg/kg	Hepatitis, peripheral neuropathy, drug fever
Rifampicin	Inhibits bacterial DNA-dependent RNA polymerase	10 mg/kg	Hepatitis, flu-like syndrome, thrombocytopenia (rare)
Ethambutol	Exact mechanism unknown. Thought to inhibit the synthesis of arabinogalactan, a mycobacterial cell wall constituent	15–20 mg/kg	Optic neuritis
Pyrazinamide	Inhibits fatty acid synthetase-I (FASI) of *M. tuberculosis*	20–25 mg/kg	Hepatitis, hyperuricemia
Streptomycin	Inhibits bacterial protein synthesis by binding directly to the 30S ribosomal subunits	0.75–1 g	Ototoxicity, vestibular damage, renal toxicity

Table 2.13 Second line drugs

Drug	Mechanism of action	Dose/day	Side effects
Levofloxacin Ofloxacin	Inhibit DNA-gyrase	500 mg 400–800 mg	CNS excitation, seizures, tendon damage in children
Para-aminosalicylic acid (PAS)	Impairment of folate synthesis and inhibition of iron uptake. PAS is a bacteriostatic drug	12 g	Diarrhea, hepatitis, hypersensitivity reactions
Ethionamide	Inhibition of the synthesis of oxygenated mycolic acid	1 g	Hepatitis
Cycloserine	Inhibits cell wall synthesis	1 g	Depression, personality changes, psychosis, convulsion
Thioacetazone	Inhibits cyclopropane mycolic acid synthases (CMASs)	150 mg	Exfoliative dermatitis, hepatitis
Kanamycin	Inhibits protein synthesis by binding to ribosomal subunit	1 g	Ototoxicity, nephrotoxicity, and vestibulotoxicity
Capreomycin	Inhibits protein synthesis by binding to ribosomal subunit. It is bacteriostatic	1 g IV or IM	Ototoxicity, nephrotoxicity, and vestibulotoxicity

Table 2.14 WHO guidelines for the treatment of tuberculosis

Category	Treatment guidelines
New patients Those who have never had treatment for TB, or have taken anti-TB drugs for less than 1 month. New patients may have positive or negative bacteriology and may have disease at any anatomical site	*Recommended regimen* 2HRZE/4HR (2 months of HRZE daily and 4 months of HR daily) *Alternative regimens* 2HRZE/4(HR)**3** (2 months of HRZE daily and 4 months of HR thrice a week, or 2(HRZE)**3**/4(HR)**3** (2 months of HRZE thrice a week and 4 months of HR thrice a week). These two are acceptable alternatives for any new TB patient receiving directly observed therapy.
Previously treated patients Those who have received 1 month or more of anti-TB drugs in the past, may have positive or negative bacteriology and may have disease at any anatomical site	In settings where rapid molecular-based drug susceptibility testing (DST) is available, the results should guide the choice of regimen. In settings where rapid molecular-based DST results are not available, empiric treatment should be started as follows: TB patients whose treatment has *failed* or other patient groups with high likelihood of MDR-TB should be started on an empirical MDR regimen TB patients returning after *defaulting* or *relapsing* from their first treatment course may receive the retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if country-specific data show low or medium levels of MDR in these patients or if such data are not available. When DST results become available, regimens should be adjusted appropriately.

DOT (Directly Observed Therapy)

- Treatment default is a major problem in TB treatment. To improve this DOT has been designed. DOT is defined as "observation of the patient by a healthcare provider or other responsible person as the patient ingests anti-TB medications." Drugs can be given only two or three times per week. DOTS refers to directly observed therapy short course.
- Although DOT programs require significant resources, they are very effective. DOT programs have been found to improve cure rate while decreasing the incidence of drug resistance and treatment failure.
- The Center for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS) recommend that DOT be considered for all patients. In addition, all patients with drug resistant tuberculosis should receive DOT. Read more details on DOT in the next page.

Monitoring Treatment

- Sputum should be examined monthly until AFB smears and cultures are negative in patients with pulmonary TB. By the end of the second month of treatment >80% of patients will have negative sputum cultures. By the end of the third month, almost all patients should be culture-negative. AFB smear becomes negative a little later than culture due to the presence of dead bacilli in the sputum. If the patient's sputum culture remains positive at ≥3 months, treatment failure and drug resistance should be suspected. If cultures cannot be done, then AFB smear examination should be done at 2, 5, and 6 months. Smears positive after 5 months are indicative of treatment failure.
- AFB smear and culture is difficult in patients with extrapulmonary tuberculosis. In these cases, the response to treatment should be assessed clinically.
- Serial chest radiographs are not recommended to monitor response to treatment, as radiographic changes may lag behind bacteriologic response. However, a chest radiograph may be obtained at the end of treatment and used for comparative purposes should the patient develop symptoms of recurrent tuberculosis months or years later.
- During treatment, patients should be monitored for drug side effects. The most important side effect is hepatitis. Baseline LFT should be done for all patients before starting ATT. LFT should be monitored monthly thereafter. Up to 20% of patients have small increases in AST (aspartate aminotransferase) up to three times the upper limit of normal without any symptoms. This is of no consequence. For patients with symptomatic hepatitis and those with marked (five- to sixfold) elevations in serum levels of AST, treatment should be stopped and drugs reintroduced one at a time after liver function tests have returned to normal.
- Pyrazinamide should be stopped if the patient develops gouty arthritis. Individuals who develop autoimmune thrombocytopenia secondary to rifampicin should not receive the drug thereafter. Similarly, the occurrence of optic neuritis with ethambutol is an indication for permanent discontinuation of this drug.

Treatment Failure and Relapse

- As mentioned above, treatment failure is suspected when a patient's sputum cultures remain positive after 3 months or when AFB smears remain positive after 5 months. In such cases a drug susceptibility test to first- and second-line agents should be done. Drug susceptibility testing takes a few weeks. Pending the results, same treatment can be continued. However, if the patient's clinical condition is deteriorating, treatment should be changed even before the susceptibility test report becomes available. If so, at least two and preferably three drugs that have never been used and to which the bacilli are likely to be susceptible should be added while continuing isoniazid and rifampicin.

Sequelae of Pulmonary Tuberculosis

- Fibrosis and destruction of the lung
- Bronchiectasis
- Lung abscess
- Aspergilloma (fungal ball)
- Scar carcinoma
- Chronic respiratory failure and cor pulmonale
- Chronic tuberculous empyema and fibrothorax
- Amyloidosis.

Prevention

- ***Early diagnosis and treatment*:** TB should be diagnosed and treated early in order to prevent deterioration of the disease and spread of the infection.
- ***Examination of close contacts*:** The close contacts of TB patients, usually the household contacts, should be examined. Tuberculin skin testing and/or chest X-ray examination is done for close contacts.
- ***Leading a healthy life style*:** Smoking alcohol intake should be stopped. Balanced diet should be taken. Adequate exercise, enough rest and sleep should be encouraged.
- ***Chemoprophylaxis*:** For household contacts of TB patients and those with AIDS infection and Hodgkin's lymphoma, isoniazid, 300 mg/day for 1 year, can reduce the incidence of tuberculosis.
- ***BCG (Bacille Calmette-Guérin) vaccination*:** All newborn babies should be vaccinated to protect them against tuberculosis.

Q. MDR tuberculosis.

Q. XDR tuberculosis.

- Multidrug-resistant tuberculosis (MDR-TB) refers to tuberculosis resistant to at least isoniazid and rifampicin, and possibly more drugs.
- Extensively drug-resistant tuberculosis (XDR-TB) refers to tuberculosis resistant to at least isoniazid, rifampin, fluoroquinolones, and either aminoglycosides (amikacin, kanamycin) or capreomycin, or both.
- Primary drug-resistance occurs in a patient who has never received antituberculosis therapy. Secondary resistance refers to the development of resistance during or following chemotherapy, for what had previously been drug-susceptible tuberculosis.

Diagnosis

- Sputum should be sent for culture and sensitivity. If a patient cannot produce sputum, sputum induction should be done by hypertonic saline nebulization. If an adequate sample is still not produced, bronchoscopy may be used to obtain sputum samples or other specimens. In extrapulmonary tuberculosis, samples of involved tissue (e.g. lymph nodes, bone, blood) should be obtained for culture and sensitivity testing as well as pathology.
- Susceptibility testing for first- and second-line agents should be performed at a reliable reference laboratory.
- There are many historical features which suggest drug-resistant tuberculosis. These include:
  - Previous treatment for active tuberculosis
  - Tuberculosis treatment failure or relapse in a patient with advanced HIV infection
  - Contact with a case of drug-resistant tuberculosis
  - Failure to respond to empiric therapy

Treatment of MDR-TB

- MDR-TB should be managed by medical personnel with expertise and experience in treating such cases. Laboratory facilities to document drug susceptibility and monitor response should be available. Each dose in an MDR regimen is given as DOT throughout the treatment
- For MDR treatment, anti-TB drugs are grouped into five groups according to efficacy, experience of use and drug class (Table 2.15). All the first-line anti-TB drugs are in Group 1, except streptomycin, which is put in Group 2 along with other injectables. All the drugs in Groups 2–5 (except streptomycin) are second-line, or reserve drugs.
- When MDR TB is suspected, sputum for culture and drug susceptibility testing (DST) should be sent and patient should be started on empirical MDR regimen till the DST results are available. For empirical MDR regimen, drugs from Groups 1–5 are selected in a hierarchical order. One or more drugs from group 1 are selected based on the likely efficacy, then an effective aminoglycoside or polypeptide by injection is added (Group 2). Then, a fluoroquinolone from Group 3 and a drug from Group 4 are added to make a regimen of at least four effective drugs.
- If the above regimen does not have at least four effective drugs, consider adding two Group 5 drugs. The empirical regimen thus chosen can have up to 7 drugs. MDR regimen can be further modified when DST results become available.
- Diagnosis and management of XDR-TB is same as MDR-TB.

Table 2.15 Groups of drugs to treat MDR-TB

Group	Drugs (abbreviations)
Group 1 First-line oral agents	Pyrazinamide (Z) Ethambutol (E) Rifabutin (Rfb)
Group 2 Injectable agents	Kanamycin (Km) Amikacin (Am) Capreomycin (Cm) Streptomycin (S)
Group 3 Fluoroquinolones	Levofloxacin (Lfx) Moxifloxacin (Mfx) Ofloxacin (Ofx)
Group 4 Oral bacteriostatic second-line agents	Para-aminosalicylic acid (PAS) Cycloserine (Cs) Terizidone (Trd) Ethionamide (Eto) Protionamide (Pto)
Group 5 Agents with unclear role in treatment of drug resistant-TB	Clofazimine (Cfz) Linezolid (Lzd) Amoxicillin/Clavulanate (Amx/Clv) Thioacetazone (Thz) Imipenem/Cilastatin (Ipm/Cln) High-dose Isoniazid (high-dose H_B) Clarithromycin (Clr)

Duration of Treatment

- In MDR-TB treatment, the intensive phase is defined by the duration of treatment with the injectable agent. The injectable agent should be continued for a minimum of 6 months, and for at least 4 months after the patient first becomes and remains smear- or culture-negative.
- Total duration of therapy depends on culture conversion. Therapy should be continued for a minimum of 18 months after culture negativity. Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage.

Monitoring of Patients on MDR Regimen

- Close monitoring is essential during treatment of MDR-TB patients. To assess treatment response, sputum smears and cultures should be done monthly until smear and culture conversion. (Conversion is defined as two consecutive negative smears and cultures taken 30 days apart.) After conversion, monitoring is at least monthly for smears and quarterly for cultures.

Adjunctive Therapies

- Some trials have shown that interferon-gamma (IFNγ) is useful in the management of MDR-TB. Interferon-gamma is normally produced by CD4+ T lymphocytes and serves to activate alveolar macrophages.

Surgery

- Surgery can be considered in patients with sputum cultures positive for longer than three months despite appropriate therapy or with isolates resistant to all of the first-line oral agents. Patients with localized pulmonary disease, which can be completely removed at operation, are most likely to benefit from surgery. However, drugs should be continued for at least 18 months after surgery.

Q. DOTS (directly observed therapy short-course).

- The WHO-recommended DOTS strategy was launched formally as Revised National TB Control programme (RNTCP) in India in 1997. Since then, it has played an important role in controlling the incidence and prevalence of TB in India. DOTS is the most effective strategy available for controlling TB.
- The five key components of DOTS are:
  - Political commitment to control TB;
  - Case detection by sputum smear microscopy examination among symptomatic patients;
  - Patients are given anti-TB drugs under the direct observation of the healthcare provider/community DOT provider;
  - Regular, uninterrupted supply of anti-TB drugs; and
  - Systematic recording and reporting system that allows assessment of treatment results of each and every patient and of whole TB control programme.
- In DOTS, the responsibility of ensuring regular and complete treatment of the patient lies with the health system.
- In DOTS the duration of treatment is 6 months, i.e. initial 2 months of intensive phase followed by 4 months of continuation phase. In the intensive phase, H, R, Z and E are administered under a direct supervision thrice weekly on alternate days for 2 months. In the continuation phase, H and R are given thrice weekly on alternate days for 4 months dosages with appropriate supervision (the first dose of each week given directly supervised and the patient self-administering next two doses of the week, at home).
- The drug administration days are fixed for a particular patient and either a Monday-Wednesday-Friday or a Tuesday-Thursday-Saturday schedule is followed. If the patient 'misses' a dose, he must be contacted within a day of the missed dose during an intensive phase and within a week of the missed dose during the continuation phase. In case of drug non-collection due to whatever reasons, the patient and the peripheral health functionary may agree on a mutually convenient location for the drug collection/administration.
- However, WHO recommends that wherever feasible, daily treatment should be used throughout the course of therapy. In HIV infected patients, DOTS should not be used.

Q. Tuberculin test (Montoux test).

- The Mantoux test is done by intradermal injection of 0.1 ml of PPD-5 (purified protein derivative of Siebert stabilized with tween 80) or 1 tuberculin unit of PPD-RT 23' into the volar aspect of the forearm.
- Test is read after 48–72 hours. If the test is positive, an induration surrounded by erythema is formed. The maximum diameter of the induration and not redness, is recorded and interpreted as follows:
  >15 mm or ulceration—strongly positive
  >10 mm—positive
  5 to 9 mm—indeterminate
  <5 mm—negative
- Its negative predictive value is higher than positive predictive value. Hence, tuberculin test is more useful to exclude the diagnosis of tuberculosis rather than to diagnose it.
- A positive reaction indicates that the individual has been exposed to mycobacterium (*M. tuberculosis*) but the individual may or may not be suffering from active disease. A strongly positive test may indicate recent infection. The test is positive in 85 percent of infected individuals.
- Ten percent of recent tuberculin converters may develop active disease in their lifetime and 5 percent do so within the first two years of infection.
- The test is of limited value in the diagnosis of active TB because of its relatively low sensitivity and specificity and its inability to discriminate between latent infection and active disease.

- It may be false negative in miliary tuberculosis, sarcoidosis, immunosuppressed conditions and viral fevers. False-positive reactions may be caused by infections with non-tuberculous mycobacteria and by BCG vaccination.

Q. Miliary tuberculosis.

Or

Q. Disseminated tuberculosis.

- Miliary tuberculosis (TB) refers to clinical disease resulting from the uncontrolled hematogenous dissemination of *Mycobacterium tuberculosis*. It is so called because of the resemblance of lesions to millet seeds.
- Miliary tuberculosis is a more common consequence of primary tuberculosis infection than reactivation. Miliary TB may occur in an individual organ (rare), in several organs, or throughout the entire body (>90%), including the brain.
- Risk factors for miliary tuberculosis include immunosuppression and conditions associated with immunosupression such as: HIV infection; cancer; transplantation; malnutrition; diabetes; end-stage renal disease. It is more common in children and very old individuals.

Clinical Features

- Symptoms are fever, night sweats, anorexia, weakness, weight loss and cough.
- Rarely elderly persons may present with intermittent fever, anemia and meningeal involvement.
- Patients may present with multiorgan dysfunction.
- Adrenal insufficiency can occur due to adrenal gland involvement.
- Examination may show hepatosplenomegaly, lymphadenopathy. Eye examination may show choroidal tubercles. Meningismus may be present in some cases.

Diagnosis

- ***Chest X-ray*:** Often shows miliary reticulonodular pattern. Pleural effusion may be present.
- ***CT chest*:** It has higher sensitivity and specificity than chest radiography in displaying randomly distributed nodules.
- ***Ultrasound abdomen*:** May reveal diffuse liver disease, hepatomegaly, splenomegaly, or para-aortic lymph nodes.
- ***Tuberculin test*:** Is frequently negative.
- ***Sputum microscopy*:** Is negative for AFB in most cases.
- ***Bronchoalveolar lavage and transbronchial biopsy*:** May be required in some cases to establish diagnosis.
- ***Liver or bone marrow biopsy*:** May show tuberculous granulomas.

Treatment

- Military tuberculosis is treated with standard anti-tuberculous therapy.

Q. Causes of hemoptysis in pulmonary tuberculosis.

- Active tuberculosis
- Reactivation of tuberculosis
- Rupture of Rasmussen's aneurysm (arises from bronchial arteries when TB extends into the adventitia and media causing thinning of the vessel wall)
- Post-tubercular bronchiectasis
- Aspergilloma invading an old healed cavity
- Scar carcinoma arising from the healed scar of TB.

Q. Fall and rise phenomenon.

- It is seen in patients who are treated with ineffective anti-tuberculous therapy.
- Initially after the commencement of treatment there is fall in sputum bacillary content. Sputum becomes negative on microscopy. Later as the treatment is continued there is again a rise in sputum bacillary content. This is called the fall and rise phenomenon.
- The "fall" happens due to the killing of drug sensitive tuberculous bacteria. The "rise" happens due to the multiplication of drug resistant bacilli as the treatment is continued.
- The fall and rise phenomenon leads to treatment failure.

Q. Extrapulmonary tuberculosis.

- Extrapulmonary tuberculosis is defined as disease outside the lung parenchyma.
- During the initial seeding of infection with *M. tuberculosis,* hematogenous dissemination of bacilli to a number of organs can occur. These localized infections can progress to primary tuberculosis or remain dormant and get activated later. Extrapulmonary tuberculosis, therefore, can either be a presentation of primary or reactivation tuberculosis.
- Extrapulmonary tuberculosis may be generalized or confined to a single organ. Extrapulmonary tuberculosis is found in 15 to 20 percent of all tuberculosis cases. The incidence is higher in young children and immunocompromised patients.
- Extrapulmonary sites most commonly involved, in descending order of frequency are:
  - Lymph nodes
  - Pleura

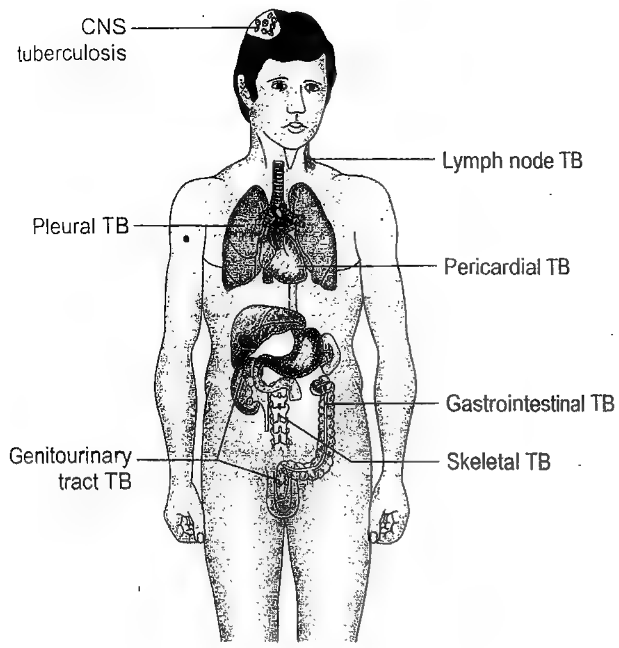

Fig. 2.4: Sites of extrapulmonary TB

- Upper airways
- Genitourinary tract
- Bones/joints
- Meninges
- Peritoneum
- Pericardium

Lymph Node TB (Tuberculous Lymphadenitis; Scrofula)

- Painless swelling of lymph nodes, usually at cervical and supraclavicular sites. Lymph nodes may be inflamed and tender and have a fistulous tract to skin draining caseous material. Systemic symptoms are usually absent except in immunocompromised patients.
- Other lymph nodes which can get involved are axillary, inguinal, mesenteric, and mediastinal lymph nodes.
- Tuberculous mediastinal lymphadenopathy can present with dysphagia, esophageal perforation and vocal cord paralysis due to recurrent laryngeal nerve involvement.

TB of Upper Airways (Epiglottis, Pharynx, Larynx)

- Clinical features include hoarseness, dysphagia and chronic productive cough.

Genitourinary Tract TB

- Clinical features include increased urinary frequency, dysuria, hematuria, flank pain. In the initial stages patients may be asymptomatic.
- In men, epididymo-orchitis and prostatitis may develop. Sinus tracts may form draining pus externally.
- In women, it may be present as pelvic pain, infertility, and menstrual abnormalities.

Skeletal TB

- Weight-bearing joints (spine, hips, and knees—in that order) are involved often.
- Spinal TB (Pott's disease, tuberculous spondylitis) often involves ≥2 adjacent vertebral bodies. Upper thoracic spine is affected commonly in children. Lower thoracic and upper lumbar vertebrae are usually affected in adults. Clinical features include back pain, low grade fever and night sweats. Spinal cord compression produces paraplegia. Kyphosis develops in advanced disease due to vertebral body collapse.
- Joint involvement leads to pain and swelling, difficulty in walking.

CNS Tuberculosis

- ***Tuberculous meningitis*:** It presents as subacute febrile illness which evolves over 1–2 weeks but may present acutely. Clinical features include headache, altered mental status (confusion/lethargy), and neck rigidity. Cranial nerve palsies may be present particularly ocular nerves. Involvement of cerebral arteries (vasculitis) leads to occlusion and focal neurological signs including stroke. Obstructive hydrocephalus can develop due to fibrin deposition in the subarachnoid space.
- ***Tuberculoma*:** Tuberculomas are caseous foci within the substance of the brain that develop from deep-seated tubercles acquired during hematogenous dissemination. They act like intracranial space occupying lesions (ICSOL) and present with seizures and focal neurological deficits.
- ***Spinal tuberculous arachnoiditis*:** It is characterized by focal inflammatory disease at single or multiple levels in the subarachnoid space producing gradual encasement of the spinal cord by a gelatinous or fibrous exudate. Patients present with signs and symptoms of nerve root and cord compression such as radicular pain, hyperesthesia or paresthesias; lower motor neuron paralysis; and bladder or rectal sphincter dysfunction. Vasculitis may lead to thrombosis of the anterior spinal artery and infarction of the spinal cord.

Gastrointestinal (GI) TB

- It can involve bowel or peritoneum.
- Bowel involvement (ileocecal region involved commonly) produces abdominal pain often mimicking appendicitis. Other features are diarrhea, obstruction, hematochezia and palpable abdominal mass. Constitutional symptoms such as fever, weight loss, and night sweats are common. Bowel wall involvement produces ulcerations/fistulae simulating Crohn's disease. Anal fistulae can develop due to rectal involvement.

- Tuberculous peritonitis produces abdominal pain, fever and ascites.

Pericardial TB (Tuberculous Pericarditis)

- Onset is usually subacute. Clinical features include fever, retrosternal pain and pericardial friction rub. Pericardial effusion may develop and lead to cardiac tamponade. Constrictive pericarditis may ultimately appear.

Less Common Sites

- ***Eyes***: Chorioretinitis, uveitis, phlyctenular conjunctivitis.
- ***Tuberculous otitis***: Hearing loss, otorrhea, tympanic membrane perforation
- ***Skin***: Abscesses, chronic ulcers, scrofuloderma, lupus vulgaris, erythema nodosum
- ***Adrenal glands***: Signs of adrenal insufficiency such as weight loss, weakness, hypotension, hyperpigmentation.

Treatment of Extrapulmonary Tuberculosis

- See WHO classification of tuberculosis and treatment.

Q. Indications for corticosteroids in tuberculosis treatment.

- There are some situations where steroids are given along with antituberculous therapy to improve the final outcome. Steroids should always be given along with ATT, otherwise the disease may worsen.

Indications

- Allergic reactions to antituberculous drugs
- Pericardial tuberculosis (reduces inflammation, scarring, amount of effusion and development of constrictive tuberculosis)
- Tuberculosis of the eye, larynx and ureteric involvement in genitourinary TB (reduces inflammation, tissue destruction and scarring)
- Tuberculous meningitis (reduces adhesions, obstructive hydrocephalus and improves final outcome)
- Adrenal tuberculosis (need to replace steroids)

Dosage

- TB meningitis requires a dose of 40 to 60 mg prednisolone per day for 4–6 weeks and then gradually tapered off.
- For other indications 10 mg of prednisolone twice daily is given for 4–6 weeks and then gradually tapered off.

Q. Discuss the etiology, clinical features, investigations and treatment of interstitial lung disease (ILD).

Q. Idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis).

- The interstitial lung diseases (ILDs) also known as diffuse lung diseases (DLD) are a heterogenous group of disorders characterized by diffuse parenchymal lung involvement. Parenchyma of the lung includes—the alveoli, the alveolar epithelium, the capillary endothelium, and the spaces between these structures.
- Interstitial lung diseases (ILD) produce a restrictive ventilatory defect without airway obstruction, decreased pulmonary diffusing capacity, and hypoxaemia.
- Two histopathological patterns of ILDs are recognized (1) those with predominant inflammation and fibrosis, and (2) those with predominant granulomatous reaction in interstitium.

Causes of ILD

- There are numerous causes of ILD. But only a few causes account for majority of ILDs. When the cause is unknown, it is called idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis).

Classification

Table 2.16 Causes of ILD

• Idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis) • Sarcoidosis • Connective tissue disease associated ILD – Systemic sclerosis – Rheumatoid arthritis – Systemic lupus erythematosus – Sjögren's syndrome – Polymyositis-dermatomyositis • Pneumoconiosis: Silicosis, asbestosis, siderosis, berylliosis, talcosis • Tropical pulmonary eosinophilia • Extrinsic allergic alveolitis; farmer's lung • Pulmonary vasculitis – Wegener's granulomatosis – Goodpasture's syndrome • Idiopathic pulmonary hemosiderosis • Pulmonary alveolar proteinosis	• Histiocytosis-X • *Infections*: – Interstitial viral pneumonias – Miliary tuberculosis – Disseminated histoplasmosis – *Pneumocystis carinii* pneumonia – Aspiration pneumonia – Following ARDS • *Radiation injury*: Radiation pneumonitis • Carcinomatosis lymphangitis • Disorders caused by inhalation of toxic gases • Oxygen toxicity • *Drugs*: Amiodarone, gold and chemotherapy drugs • *Poisons*: Paraquat

Clinical Features

- Chronic dyspnea (most common complaint). Dyspnea is progressive and worsened by exertion. Sudden worsening of dyspnea, especially if associated with acute chest pain, may indicate spontaneous pneumothorax.
- Dry cough
- Wheezing and chest pain are rarely seen.
- There may be h/o occupational exposure to organic or inorganic dust.
- General examination may show clubbing, cyanosis, tachypnea, and use of accessory respiratory muscles.
- Examination of the chest may show decreased expansion bilaterally and fine, dry end inspiratory crepitations may be heard bilaterally usually at the base of the lungs. Advanced disease may show findings of pulmonary hypertension and cor pulmonale.
- In addition to the above findings patients may have features of underlying disease causing ILD. For example, patients with systemic sclerosis may have Raynaud's phenomenon; those with rheumatoid arthritis may have joint involvement. Those with SLE may have malar rash.

Investigations

Chest X-ray

- Reticulonodular shadows and honeycombing may be seen diffusely and bilaterally more in basal areas.
- Chest X-ray may also show features of underlying disease. For example, bilateral hilar lymphadenopathy may be seen in sarcoidosis and egg-shell calcification of hilar lymph may be seen in silicosis.

CT Scan

- HRCT (high resolution computed tomography) is superior to chest X-ray for early detection and confirmation of ILD. It shows the reticulonodular pattern and honeycombing. It can also identify any underlying disease like sarcoidosis better than chest X-ray. HRCT allows better assessment of the extent and distribution of disease. If lung biopsy is planned, HRCT is useful to know from which area biopsy should be taken.

Lung Biopsy

- Lung biopsy is the most definitive method for diagnosing ILD. Biopsy should be done before starting treatment. Fiberoptic bronchoscopy with multiple transbronchial lung biopsies (four to eight samples) is the procedure of choice. If a specific diagnosis is not possible by transbronchial biopsy, then surgical lung biopsy by video-assisted thoracic surgery or open thoracotomy is indicated.

Pulmonary Function Tests

- Spirometry shows a restrictive defect with reduced total lung capacity (TLC), functional residual capacity, and residual volume. FEV_1 and forced vital capacity (FVC) are reduced due to decreased TLC. The FEV_1/FVC ratio is usually normal or increased.
- Diffusing capacity of the lung for carbon monoxide (D_{LCO}) is decreased.
- Arterial blood gas analysis may reveal hypoxemia and respiratory alkalosis (due to hyperventilation). CO_2 retention occurs in end-stage disease.

Other Investigations

- Investigations to find out the cause for ILD should be done based on clinical features of the patient.
- ANA should be done if SLE or other connective tissue disease is suspected. RA factor may be positive in rheumatoid arthritis. Antineutrophilic cytoplasmic antibodies (ANCA) may be positive in Wegener's granulomatosis. Patients with extrinsic allergic alveolitis have precipitable antibodies against the offending antigen.
- Lymph node biopsies are helpful in diagnosing tuberculosis, sarcoidosis or histiocytosis-X.

Treatment

- ILD progresses slowly and results in respiratory failure. Treatable causes should be identified and treated. Treatment is mainly directed at suppressing inflammatory process, thereby reducing further lung damage. Existing fibrosis cannot be reversed by treatment.
- Glucocorticoids are the mainstay of therapy, but the success rate is low. A common starting dose is, prednisolone 0.5 to 1 mg/kg once daily orally. This dose is continued for 1 to 3 months, and the patient is reassessed. If the patient is stable or improved, the dose is tapered to 0.25 to 0.5 mg/kg and is maintained at this level for an additional 1 to 3 months. If the patient's condition continues to worsen even on glucocorticoids, another drug (cyclophosphamide or azathioprine) is added. If all these therapies fail, lung transplantation may be considered.
- Hypoxemia (PaO_2 <55 mm Hg) should be managed by supplemental oxygen.

Q. Cystic fibrosis.

- The first known reference to CF is an adage from northern European folklore: "Woe to that child which when kissed on the forehead tastes salty. He is bewitched and soon must die." This saying describes the salty sweat that is the basis of an important diagnostic test and early mortality of cystic fibrosis.

- Cystic fibrosis (CF) is a genetic (monogenic) disorder that presents as a multisystem disease. It is characterized by recurrent airway infection (which leads to bronchiectasis), exocrine pancreatic insufficiency and intestinal dysfunction, abnormal sweat gland function, and urogenital dysfunction.
- It usually presents in childhood but some patients may present in adulthood.
- Earlier, patients used to die in childhood but now because of improvement in therapy patients reach more than 30 years of age. Pulmonary involvement occurs in 90% of patients surviving the neonatal period. End-stage lung disease is the principal cause of death.

Pathogenesis

- Cystic fibrosis (CF) is an autosomal recessive disease resulting from mutation in a gene located on chromosome 7. Mutation in this gene leads to absent or defective CF transmembrane conductance regulator (CFTR). The CFTR protein functions both as a cyclic AMP-regulated Cl^- channel and as regulator of other ion channels. CFTR is located in the apical (lumen-facing) membrane of epithelium in the airways, pancreatic ducts, intestine, biliary ducts, and in the apical and basolateral membranes of the sweat gland duct.
- Normally the sweat gland duct absorbs Na through Na^+ channels and Cl^- through CFTR Cl^- channels as sweat flows through it. In CF, loss of CFTR prevents absorption of Cl^-, which in turn, prevents absorption of Na^+ to maintain electroneutrality. As a result, sweat contains high Na^+ and Cl^- concentrations.
- In the exocrine pancreas, the absence of the CFTR Cl^- channel in the apical membrane of pancreatic ductal epithelial cells interferes with secretion of Na^+ and bicarbonate into the duct. The failure to secrete Na^+ and bicarbonate and water leads to retention of enzymes in the pancreas and ultimately destruction of pancreas.
- In the liver, loss of CFTR Cl^- channels disrupts normal salt and water balance in the small biliary ducts, and causes obstruction.
- Obstruction of the small ducts in the male genital tract also leads to the atrophy, fibrosis, or absence of the vas deferens, tail and body of the epididymis, and seminal vesicles.
- In the ileum, disruption of salt and water secretion produces thick, dehydrated intestinal contents that obstruct the ileum in the newborn, causing meconium ileus and producing meconium ileus-equivalent later in life.
- Repeated infections of the airways may be due to impairement of local defence mechanisms due to high NaCl concentration in the mucosa, reduced mucociliary clearance, and defective phagocytosis of bacteria. Thick, viscous, purulent sputum is formed that obstructs airways and lead to bronchiectasis.

Clinical Manifestations

- Patients with CF can present at several ages with a variety of clinical manifestations.
- Newborns may present with meconium ileus, infants and children may present with failure to thrive, and older children and adults may present with recurrent respiratory tract infections.
- Pancreas involvement leads to fat and protein malabsorption. Patients have steatorrhea. Children may present with failure to thrive. Generalized edema can occur due to hypoproteinemia.
- Cough is the common manifestation of respiratory system involvement due to recurrent infections. Episodes of cough tend to persist longer than expected for an acute respiratory illness and, with time, occur more and more frequently. Sputum is thick, purulent, and often green colored due to pseudomonas infection. With recurrent infections patient develops symptoms of bronchiectasis.
- Other features are infertility due to genitourinary tract involvement and cholelithiasis due to biliary tract involvement.

Investigations

- The diagnosis of CF is by a combination of clinical criteria and analyses of sweat Cl^- values. If sweat Cl^- concentration is >70 mEq/L, it suggests cystic fibrosis.
- Genetic testing—for the presence of CFTR gene mutation can also be done to diagnose CF.
- The nasal transepithelial potential difference is raised in CF.
- Other useful tests include chest X-ray, CT chest, pulmonary function tests, etc.

Treatment

Antibiotics

- Lung infections require an intensive course of parenteral antibiotics for 2 to 3 weeks. The choice of antibiotics is based on sputum cultures and sensitivity. Since *P. aeruginosa* is a particularly common pathogen, a combination of an aminoglycoside and a beta-lactam antibiotic are commonly used.

Chest Physiotherapy

- Chest percussion and postural drainage are helpful in clearing purulent secretions.

Bronchodilators

- Bronchodilator therapy should be considered during exacerbations and in hospitalized patients.

Deoxyribonuclease

- DNA released from neutrophils forms long fibrils which increases the viscosity of sputum. Deoxyribonuclease can cleave DNA and decrease sputum viscosity which helps in clearance of sputum by cough.

Pancreatic Enzymes

- Since pancreatic enzymes are deficient in cystic fibrosis, pancreatic enzyme supplementation (lipase, trypsin) at mealtimes is recommended. The fat-soluble vitamins A, D, and E are also given daily since they also require pancreatic enzymes for absorption. Vitamin K may be given as required based on prothrombin time.

Ivacaftor

- The cystic fibrosis transmembrane conductance regulator (CFTR), ivacaftor, has been shown to improve lung function, reduce the risk of pulmonary exacerbations, and reduce the concentration of sweat chloride.

Gene Therapy

- The best approach to treat this disease would be to transfer a normal CFTR gene or cDNA into the affected cells. Progress in this area of research has been substantial and it is hoped that successful gene therapy will become a reality.

Other Supportive Measures

- Hypertonic saline inhalation has been shown to increase hydration of airway surface liquid in patients with CF and improves lung function plus reduces recurrent pulmonary exacerbations. Adequate salt should be taken during hot weather since excess salt is lost in the sweat. Adequate immunizations, including influenza, and pneumococcus are mandatory. Smoking should be avoided. Lung transplantation should be considered for patients with an FEV_1 less than 30% predicted.

Q. Pneumoconioses.

- Pneumoconioses (dusty lungs) refer to a group of lung diseases caused by inhalation of inorganic dust. After inhalation, dust particles get deposited in the alveoli and cause inflammation and fibrosis (interstitial fibrosis).
- The principal cause of the pneumoconioses is workplace exposure; environmental exposures have rarely given rise to these diseases.
- Pneumoconioses many years to develop and manifest, although in some cases—silicosis, particularly—rapidly progressive forms can occur after only short periods of intense exposure. When severe, the diseases often lead to lung impairment, disability, and premature death. From a public health perspective, these conditions are entirely man-made, and can be avoided through appropriate dust control.
- Other forms of pneumoconioses can be caused by inhaling dusts containing aluminum, antimony, barium, graphite, iron, kaolin, mica, talc, among other dusts. Overall, most physicians do not encounter these diseases very frequently. Byssinosis, caused by exposure to cotton dust, is sometimes included among the pneumoconioses, although its pattern of lung abnormality is different from the pneumoconioses listed here.
- **Common causes of pneumoconiosis (Table 2.17):**

Table 2.17 Common causes of pneumoconiosis

Pneumoconiosis	Caused by
Silicosis	Silica dust
Asbestosis	Asbestos
Coal workers pneumoconiosis	Coal dust
Berylliosis	Beryllium
Siderosis	Iron oxide
Stannosis	Tin oxide

Q. Silicosis.

- Silicosis is the most common occupational lung disease caused by inhalation of crystalline silica (alpha-quartz or silicon dioxide). Silicosis occurs in people working in mining, quarrying, sandblasting, masonry, founding, and ceramics.
- Silica (silicon dioxide) is the most abundant mineral on earth. Silica exists in both crystalline and amorphous forms. Amorphous forms are relatively nontoxic. Crystalline silica causes pneumoconiosis after inhalation.
- Crystalline forms of silica include quartz, cristobalite, and tridymite. Quartz is the most common type, and is found in rocks including granite, slate, and sandstone. Cristobalite and tridymite occur naturally in lava and are formed when quartz or amorphous silica is subjected to very high temperatures.

Pathogenesis

- After inhalation, silica particles are deposited in the distal airways. Alveolar macrophages ingest the silica particles and may migrate into the interstitium. Then they enter the lymphatics and are transported to the regional lymph nodes. Macrophages may release proteolytic enzymes

and cytokines which attract other inflammatory cells such as neutrophils and T-lymphocytes. Macrophages also cause lung injury by release of superoxide anions and hydroxyl radicals. The result of all this is inflammation, fibrosis and production of silicotic nodules.

Clinical Presentation and Investigations

Acute Silicosis

- Occurs after exposure to high concentrations of crystalline silica. Symptoms develop within a few weeks to a few years after the exposure. It is characterized by rapid onset of symptoms including cough, weight loss, fatigue, and sometimes pleuritic pain. Examination may show lung crepitations and rhonchi. The prognosis of patients with acute silicosis is very poor. Patients die of respiratory failure usually within four years after the onset of symptoms. Mycobacterial and fungal infections frequently complicate the clinical course.

Chronic Silicosis

- It develops slowly, usually appearing 10 to 30 years after first exposure. Symptoms are chronic dyspnea, cough and sputum production.
- Severe lung disease may lead to corpulmonale with associated right ventricular heave, raised JVP, hepatomegaly, and peripheral edema.

Investigations

- ***Chest X-ray:*** Most commonly silicosis is diagnosed by a routine chest radiograph. Chest X-ray shows round opacities ranging from 1 to 10 mm size seen predominantly in the upper lung zones initially and in advanced disease all over the lungs. Progressive massive fibrosis (PMF) manifests as bilateral upper lobe masses, which are formed by the coalescence of nodules. The hilar lymph nodes may show 'egg shell calcification'.
- ***CT/HRCT chest:*** This is more sensitive than chest X-ray in picking up nodules, fibrosis and pleural thickening.
- ***Pulmonary function tests*:** Show restrictive ventilatory impairment and arterial hypoxemia. Advanced disease may cause pulmonary HTN, cor pulmonale and respiratory failure.
- ***Lung biopsy*:** This is usually not necessary because diagnosis can be made by clinical features and above investigations. However, if the diagnosis is in doubt, lung biopsy may be considered.
- ***Tuberculin skin test*:** Using purified protein derivative (PPD) is indicated in all persons with silicosis as they are prone to develop tuberculosis.

Treatment

- There is no specific treatment for silicosis. Patient should be advised to avoid further exposure to silica dust and quit smoking.
- Bronchodilators may be helpful to relieve bronchial obstruction.
- Corticosteroid therapy (prednisolone) has been shown to produce significant improvements in lung volumes, carbon monoxide diffusing capacity, and partial pressure of arterial oxygen.
- Lung transplantation should be considered in end-stage silicosis with respiratory failure.
- Experimental approaches to treatment include whole-lung lavage and aluminum inhalation.

Prevention

- Silicosis can be prevented by controlling the dust levels at work, and by providing exhaust ventilation at points of dust generation.

Q. Coal worker's pneumoconiosis (CWP).

Etiology

- Coal workers' pneumoconiosis (CWP) is a parenchymal lung disease caused by inhaling coal mine dust. Anthracosis is the asymptomatic accumulation of carbon without a consequent cellular reaction. Such accumulation can be found in most urban dwellers and tobacco smokers. Inhaled coal dust becomes a problem when body reacts to it with consequent fibrosis in the lungs.
- Coal refers to a group of carbonaceous materials characterized by the hardness or "rank," ranging from peat, the softest, to anthracite, the hardest. The risk of CWP increases with dust level in the mine and cumulative exposure to coal mine dust. The risk is more with harder coals.
- Lung diseases caused by coal mine dust are also referred to as "black lung." CWP is called "simple" if all radiographic opacities are less than 1 cm in diameter. If any opacity is 1cm or more on chest X-ray, it is termed progressive massive fibrosis (PMF). Exposure to coal mine dust is also associated with bronchitis.

Pathology

- The inhaled coal dust causes an inflammatory reaction in the lungs leading to accumulation of macrophages and other inflammatory cells. Chronic inflammation leads to fibrosis. The characteristic lesion of CWP is coal macule, which is focal collection of coal dust and pigment-laden macrophages. As these macules extend, they join other macules in the vicinity, forming discrete

areas of interstitial fibrosis. This growing collagen network causes distention of the respiratory bronchioles, forming focal areas of emphysema (commonly centrilobular emphysema).

- Macules may arrest or may enlarge and form nodules which may join together to produce progressive massive fibrosis. Progressive massive fibrosis is diagnosed pathologically if nodules reach at least 2 cm, (or X-ray wise 1 cm or more). These lesions are rich in collagen and disrupt the lung's architecture.
- Progressive massive fibrosis in association with rheumatoid arthritis is known as Caplan syndrome and is characterized by multiple nodules, ranging from 1 to 5 cm, in the periphery of lungs.

Clinical Manifestations

- Many patients are asymptomatic in early stages of disease and incidentally diagnosed by chest X-ray.
- Patients may present with cough and black sputum production.
- Dyspnea may occur in advanced disease.
- Severe lung disease may lead to corpulmonale with associated right ventricular heave, raised JVP, hepatomegaly, and peripheral edema.

Investigations

- ***Chest X-ray***: In simple disease, the chest radiograph typically shows small nodules that tend to predominate in the upper lung zones. Reticular opacities may also be present, more often in cigarette smokers. X-ray findings and clinical symptoms do not correlate with each other because there can be significant symptoms with a little or no radiographic abnormality. Progressive massive fibrosis is associated with progressive dyspnea, pulmonary hypertension, corpulmonale and respiratory failure.
- ***Other tests***: See silicosis.

Treatment

- See silicosis.

Prognosis

- Simple pneumoconiosis alone does not increase mortality. Progressive massive fibrosis is associated with more severe morbidity and increased overall mortality.

Q. Beryllium disease.

- Beryllium is used in industries because of its light weight and high tensile strength. Exposure to beryllium occurs in aerospace, electronics and ceramic industries. Other beryllium using industries are computer, jewelry making and dental alloy/appliances.

Pathogenesis

- Inhaled beryllium elicits inflammation and chemical pneumonitis in the acute form. In chronic form it acts as an antigen and elicits cell mediated delayed type of hypersensitivity reaction leading to formation of noncaseating granulomas. Beryllium is transported to extrapulmonary sites such as the liver, spleen, skin and lymph nodes where granulomas are formed.

Clinical Features

- Acute beryllium disease occurs from exposure to a high concentration of dust or fumes. Patient presents with pharyngitis, tracheobronchitis and chemical pneumonitis. Chest X-ray shows diffuse or localized infiltrate.
- Chronic beryllium disease resembles sarcoidosis and is characterized by formation of granulomas in the lung and other organs. Patients present with exertional dyspnea, dry cough, weight loss, fatigue, and chest pain. Physical examination shows crepitations in the lungs, lymphadenopathy, hepatosplenomegaly, and skin rash.

Investigations

- Chest X-ray may show reticulonodular opacities and hilar adenopathy. In advanced disease there is honeycomb appearance of lung.
- Pulmonary function studies show a restrictive ventilatory defect and decrease in diffusion capacity.
- Beryllium-specific lymphocyte transformation test is helpful to differentiate from sarcoidosis. This test demonstrates the proliferation of lymphocytes from blood or lungs in response to beryllium salts *in vitro*.

Treatment

- Consists of removal from exposure, oxygen and corticosteroids for both acute and chronic beryllium disease.

Q. Asbestosis.

Definition

- Asbestosis specifically refers to the pneumoconiosis caused by inhalation of asbestos fibers. The disease is characterized by slowly progressive, diffuse pulmonary fibrosis.

Etiology

- The word asbestos is derived from greek and means inextinguishable. The term refers to a group of naturally occurring, heat-resistant fibrous silicates. Asbestos is used in insulation, reinforcing materials, and friction products. Asbestos fibres may be curved and flexible (serpentine) or straight and stiff (amphibole). Chrysotile

(white asbestos) is an example of serpentine and crocidolite (blue asbestos) and amosite (brown asbestos) are examples of amphibole. Chrysotile can undergo dissolution in tissues. All types of asbestos fibers are associated with asbestosis, pleural disease, and lung cancer.

Epidemiology

- People working in asbestos mines, textiles and brake lining factories, construction trades and workers using insulators are exposed to asbestos. Since a large number of buildings now have asbestos-containing materials, maintenance and demolition workers also get exposed to asbestos. However, exposure of building occupants to asbestos is quite low. The risk of asbestosis increases with cumulative exposure to asbestos fibers and manifestations usually appear after 15 to 20 years of exposure.

Pathology

- After inhalation asbestos fibers get deposited in the small airways (alveolar ducts, and peribronchiolar regions). Macrophages are attracted to these sites and an inflammatory reaction begins which results in fibrosis. Initially this fibrotic reaction is found in small airways but later involves the whole lung. In advanced cases, extensive fibrosis destroys the normal architecture of the lung and causes honeycombing (cystic spaces bounded by fibrosis). Lungs become small and stiff with macroscopically visible fibrosis and honeycombing. Asbestos bodies are visible under microscopy.

Clinical Manifestations

- Patients present with dry cough and exertional dyspnea. Fine crepitations are heard on auscultation of the chest in basal areas bilaterally. Cyanosis and clubbing may be present in advanced cases. Involvement of small airways produces airflow obstruction.
- In advanced cases, features of corpulmonale such as right ventricular heave, raised JVP, hepatomegaly, and peripheral edema may be present.

Investigations

- Chest X-ray shows irregular opacities most prominent in the basal areas. Pleural thickening and calcified pleural plaques may also be present.
- High-resolution CT is more sensitive to detect the pleural and pulmonary disease.
- Spirometry typically shows a reduced forced vital capacity (FVC) with preservation of the ratio of the forced expiratory volume in 1 second (FEV_1) to FVC, and reduced TLC and diffusing capacity.
- Lung biopsy is usually not required but can help in definitive diagnosis. Both fibrosis and asbestos bodie can be visualized through microscopy.

Treatment

- There is no specific treatment for asbestosis. Further exposure should be avoided. Oxygen supplementation is needed if there is hypoxemia. Smoking should be stopped. Lung transplantation may be considered for advanced disease.

Q. Write a brief note on obesity-hypoventilation syndrome (Pickwickian syndrome).

- Obesity hypoventilation syndrome (OHS) exists when an obese individual (body mass index >30 kg/m^2) develops awake alveolar hypoventilation ($PaCO_2$ >45 mm Hg). Other conditions which cause alveolar hypoventilation such as pulmonary disease, skeletal restriction, neuromuscular weakness, hypothyroidism, or pleural pathology should be ruled out before diagnosing OHS.
- Obesity is the hallmark of OHS (BMI >30 kg/m^2) and the prevalence of this disorder increases with increasing BMI. About 90 percent of OHS individuals will have coexisting obstructive sleep apnea (OSA).

Pathophysiology

- Obesity puts extra mechanical load on rib cage and abdomen and reduces the compliance of the chest wall. As a result the FRC (functional residual capacity) is reduced, particularly on lying down.
- Most patients have a defect in the central respiratory control system. These patients have been shown to have a decreased responsiveness to carbon dioxide rebreathing, hypoxia, or both.
- Chronic hypercapnia and hypoxemia leads to polycythemia, pulmonary hypertension and cor pulmonale.

Clinical Features

- Patients are usually middle-aged and very obese. Both sexes are equally affected. Patients are usually hypersomnolent and fall asleep when inactive. There may be cyanosis, secondary polycythemia, and cor pulmonale.

Investigations

- Chest X-ray reveals cardiomegaly.
- ECG shows evidence of right ventricular hypertrophy.
- ABG may show hypoxemia and hypercapnia (type II respiratory failure).
- A nocturnal polysomnogram shows high frequency of sleep apnea in these patients.

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Treatment

- The most important measure is to make the patient lose weight.
- Use of sedatives, and alcohol should be avoided because they aggravate hypoventilation.
- Oral medroxyprogesterone acetate and acetazolamide can be used to increase respiratory drive.
- Noninvasive ventilation using nocturnal bilevel positive-pressure ventilation (PPV) can be used in patients with chronic respiratory failure.

Q. Sleep apnea.

Q. Obstructive sleep apnea.

Q. Central sleep apnea.

- Sleep apnea is defined as intermittent cessation of the airflow at the nose and mouth during sleep for at least 10 seconds. Most patients have apnea for 20 to 30 seconds, and it may even last as long as 2–3 minutes.
- Sleep apnea has been classified into 2 types:
  1. Obstructive sleep apnea (OSA)
  2. Central sleep apnea (CSA)

1. Obstructive Sleep Apnea (OSA)

- Obstructive sleep apnea (OSA) is a sleep disorder that involves cessation or significant decrease in airflow in the presence of breathing effort. In this disorder airflow ceases because of occlusion of the upper airway, usually at the level of the oropharynx. The respiratory drive is normal.
- The obstruction results in progressive asphyxia until there is a brief arousal from sleep, whereupon the airway patency is restored and airflow resumes. The patient again returns to sleep. This sequence of events may occur many times in the night causing fragmentation of sleep which causes daytime somnolence.
- The upper airway collapses because of pressure drop during inspiration that exceeds the ability of airway dilator and abductor muscles to keep the airway open. During deep sleep there is reduced activity of muscles of the upper airway resulting in airway collapse. In many patients upper airway may be structurally narrow due to enlarged adenoids, and obesity. Thus obesity is an important cause of obstructive sleep apnea.

Criteria for diagnosing obstructive sleep apnea

Episodes of upper airway obstruction during sleep result in recurrent arousals associated with:

Excessive daytime sleepiness, unexplained by other factors, and two or more of the following:

- Loud disruptive snoring
- Nocturnal choking/gasping/snort
- Recurrent nocturnal awakening
- Unrefreshing sleep
- Daytime fatigue
- Impaired concentration

and

Overnight sleep monitoring documenting >5 episodes of hypopnea and apnea per hour

Clinical Features

- Many patients have snoring which precedes the onset of OSA by many years. Snoring is also due to narrowing of the upper airways during sleep. However, snoring alone does not warrant an investigation for OSA.
- Patients are usually obese and are between 30 and 60 years of age. Patients complain of daytime somnolence, intellectual impairment, memory loss, personality disturbances and impotence due to fragmentation of sleep.
- There may be cyclical slowing of the heart rate to 30–50 beats/minute followed by tachycardia of 90–120 beats/minute during apnea episodes. Asystole or dangerous arrhythmias can occur during the hypoventilatory phase.
- Some patients develop pulmonary hypertension, right ventricular failure, and secondary polycythemia.

Investigations

- Polysomnography is the definitive investigation of choice. It is a detailed overnight sleep study that includes recording of multiple parameters simultaneously. These include ECG to detect arrhythmias, electroencephalogram (EEG) to know sleep stages, the chin electromyogram (activity decreases in REM), and the electro-oculogram (EOG) to detect REM sleep. Pulse oximetry can be used to know oxygen saturation during apnea episodes.

Treatment

- ***General***: Weight reduction if obese, avoidance of alcohol and CNS depressant drugs, and avoidance of sleeping in the supine position.
- ***Oral appliance therapy***: Oral appliances act by moving (pulling) the tongue forward or by moving the mandible and soft palate anteriorly, enlarging the posterior airspace. They open or dilate the upper airway.
- ***Specific***: Nasal CPAP (continuous positive airway pressure) ventilation is the definitive treatment for OSA. It prevents upper airway occlusion by splinting the

pharyngeal airway with a positive pressure delivered through a nose mask. If patients cannot tolerate CPAP, surgical procedures aimed at increasing the upper airway dimensions (uvulopalatopharyngoplasty, linguoplasty, mandibular advancement), etc. can be considered. Tracheostomy should be considered in patients with severe OSA.

Central Sleep Apnea (CSA)

- Central sleep apnea is due to transient abolition of central drive to the ventilatory muscles.
- This usually happens due to fall of PCO_2 during sleep below the critical level required for respiratory stimulation. As a result apnea develops until PCO_2 rises and again stimulates respiration.

Causes of CSA

- Central respiratory drive can be abnormal in CNS diseases like brainstem tumor, infarction, or infection, Parkinson disease, encephalitis and high cervical cord compression.
- Primary central sleep apnea
- Diabetes mellitus
- Hypothyroidism
- Heart failure
- Use of opiates and other CNS depressants.

Clinical Features

- Patients complain of sleeping poorly, nocturnal awakenings, morning headache, daytime fatigue and sleepiness.
- Patients may also present with history of recurrent respiratory failure, polycythemia, pulmonary hypertension and right-sided heart failure.

Investigations

- Polysomnography is the investigation of choice and shows recurrent apnea with absent respiratory effort (whereas respiratory effort is present in obstructive sleep apnea).

Treatment

- Patients with hypoxemia benefit from nocturnal supplemental oxygen.
- Respiratory stimulation with acetazolamide or theophylline may help but results are variable and efficacy has not been established.
- Nasal CPAP (as for OSA) can be effective, although the treatment is less well-tolerated than in patients with OSA.

Q. Enumerate causes of pleural effusion. Give the differential diagnosis, clinical features, investigations, and management of pleural effusion.

- A pleural effusion is an abnormal collection of fluid in the pleural space resulting from excess fluid production or decreased absorption or both.
- Normally about 10 to 20 ml of fluid is present in the pleural space which is similar in composition to plasma except low protein (<1.5 gm/dl). Pleural fluid accumulates as a result of:
  1. Increase in vascular permeability (pneumonia)
  2. Increase in hydrostatic pressure (cardiac failure)
  3. Decrease in pleural pressure (atelectasis)
  4. Decrease in plasma osmotic pressure (nephrotic syndrome)
- Pleural effusion can be exudative or transudative based on light's criteria

Light's criteria to distinguish pleural transudate from exudate:

Pleural fluid is an exudate if one or more of the following criteria are met:
- Pleural fluid protein: Serum protein ratio >0.5
- Pleural fluid LDH: Serum LDH ratio >0.6
- Pleural fluid LDH > two-thirds of the upper limit of normal serum LDH

Causes of Pleural Effusion

Transudative Pleural Effusion

- Congestive heart failure
- Cirrhosis with portal HTN
- Nephrotic syndrome
- Peritoneal dialysis
- Hypoalbuminemia
- Atelectasis
- Constrictive pericarditis
- Superior vena caval obstruction

Exudative Pleural Effusion

- Pneumonia
- Tuberculosis
- Subphrenic abscess
- Hepatic abscess
- Esophageal perforation
- Malignancy
- Pancreatitis (acute, chronic)
- Pulmonary embolism
- Sarcoidosis

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- Acute respiratory distress syndrome (ARDS)
- Connective tissue diseases (SLE, rheumatoid arthritis)
- Hypothyroidism
- Ovarian hyperstimulation syndrome
- Chylothorax
- Meig's syndrome

Clinical Features

- Patients may be asymptomatic in mild pleural effusion.
- ***Dyspnea***: Is the most common symptom associated with effusion.
- ***Cough***: Cough is often mild and nonproductive. More severe cough with sputum suggests an underlying pneumonia or endobronchial lesion.
- ***Chest pain***: Chest pain indicates pleural irritation, and occurs in pleural infection, mesothelioma, or pulmonary infarction. Pain is pleuritic in nature and is typically described as sharp or stabbing and is exacerbated with deep inspiration. Pain may be localized to the chest wall or referred to the ipsilateral shoulder or upper abdomen because of diaphragmatic irritation. Pain may diminish as the pleural effusion increases which separates inflammed pleural surfaces from each other.
- ***Other symptoms***: Symptoms of underlying disease may be present. Lower limb edema, orthopnea, and paroxysmal nocturnal dyspnea may suggest congestive cardiac failure as the cause of pleural effusion. Night sweats, fever, hemoptysis, and weight loss should suggest TB. Hemoptysis also suggests the possibility of malignancy or endobronchial pathology, or pulmonary infarction. An acute febrile episode, purulent sputum production, and pleuritic chest pain may suggest effusion associated with pneumonia (synpneumonic effusion).
- Examination shows decreased chest movements, stony dull percussion note, and absent breath sound on the affected side. Vocal fremitus and vocal resonance are decreased. Pleural rub may be heard sometimes. Mediastinal shift may be seen in massive pleural effusion. There may be signs and symptoms of underlying disease causing pleural effusion. Peripheral edema, distended neck veins, and S_3 gallop suggest congestive cardiac failure. Presence of jaundice and ascites suggest liver disease (cirrhosis with portal HTN). Lymphadenopathy or a palpable mass suggests malignancy.

Investigations

- ***Chest X-ray***: Pleural effusion appears as a curved shadow at the lung base, blunting the costophrenic angle and ascending towards the axilla on the erect PA chest X-ray. Minimum 200 ml of fluid is required to produce a shadow on chest X-ray, but smaller effusions can be identified by ultrasound or CT scanning.
- ***Ultrasound chest***: Is more accurate than chest X-ray to detect pleural effusion. It can also be used to guide pleural aspiration and pleural biopsy. It can also distinguish pleural fluid from pleural thickening.
- ***CT scan***: It is better than both X-ray and ultrasound in showing pleural abnormalities and underlying disease. It is also helpful to distinguish benign from malignant pleural disease.
- ***Pleural fluid aspiration and analysis***: If the cause of effusion is obvious (e.g. left ventricular failure), it may not be necessary to do diagnostic pleural aspiration. Most bilateral pleural effusions are transudates and do not require aspiration for analysis. However, if the cause is not obvious and effusion is unilateral, aspiration is necessary to establish a diagnosis.
- Color and texture of fluid can give clue about the possible diagnosis. It is straw colored in transudates, turbid and purulent in empyema and hemorrhagic in pulmonary infarction or malignancy. A milky, opalescent fluid suggests a chylothorax. Black pleural fluid is seen in infection with *Aspergillus niger* or *Rhizopus oryzae*, malignant melanoma, and charcoal-containing empyema.
- Biochemical analysis allows classification into transudate and exudates (*see* Light's criteria). Measurement of adenosine deaminase level (ADA) in pleural fluid is very helpful in the diagnosis of tuberculosis. ADA level of >50 U/L is highly suggestive of TB. Increased interferon-gamma concentrations (>140 pg/ml) also support the diagnosis of tuberculous pleuritis. Increased triglyceride and cholesterol levels are seen in chylothorax. Increased amylase level is seen in effusion due to pancreatitis. A low pH suggests infection but may also be seen in rheumatoid arthritis, and ruptured esophagus.
- Microbiological investigations should be done such as Gram's stain, culture sensitivity and AFB stain. PCR for tuberculosis should be done in most cases of pleural effusion.
- Cell count, cell type and malignant cytology should also be requested.
- ***Pleural biopsy***: Combining pleural aspiration with biopsy increases the diagnostic yield. An Abrams needle is used for pleural biopsy. Pleural biopsy is better obtained under ultrasound or CT guidance. Video-assisted thoracoscopy allows the operator to directly visualize the pleura and obtain biopsy.

Management

- Asymptomatic transudative effusions need not be drained.
- *Therapeutic aspiration* should be considered in symptomatic patients (e.g. dyspnea).

- *Tube thoracostomy*: Insertion of intercostal drainage tube (ICD) is required in complicated parapneumonic effusions and empyema.
- *Pleurodesis*: Involves instilling an irritant (such as talc, doxycycline) into the pleural space to cause inflammatory changes that result in bridging fibrosis between the visceral and parietal pleural surfaces, obliterating the pleural space. Pleurodesis is used for recurrent malignant effusions.
- *Treatment of the underlying cause*: For example, heart failure, nephritic syndrome, pneumonia, etc. will often be followed by resolution of the effusion.

Q. Bronchogenic carcinoma (lung cancer).

Q. Paraneoplastic syndrome.

- The term lung cancer is used for tumors arising from the respiratory epithelium (bronchi, bronchioles, and alveoli).
- Bronchogenic carcinoma can be divided into the following types:
  - ***Small cell lung cancer (SCLC) (oat cell carcinoma)***
  - ***Non-small cell lung cancer (NSCLC)***
    - Adenocarcinoma
    - Squamous cell carcinoma
    - Large cell carcinoma
- NSCLC accounts for approximately 85% of all lung cancers. Identifying the type of cancer is important, because SCLC has a high response rate to chemotherapy and radiation, whereas NSCLC can be cured by surgery in certain stages and is not curable by chemotherapy alone.

Incidence and Prevalence

- Bronchogenic carcinoma is the most common cancer in men. It is one of the leading causes of cancer death in both men and women. The incidence of lung cancer peaks between ages 55 and 65 years.
- Males are affected more often than females probably due to smoking habits. However, incidence in females is also increasing because of increased smoking habits in women also.
- Incidence is higher in urban than in rural areas, probably due to air pollution. The precise incidence of lung cancer in India is not known.
- Adenocarcinoma, arising from the bronchial mucosal glands, is the most common NSCLC cancer in the United States (35–40% of all lung cancers). *Squamous cell carcinoma is the next common carcinoma.*

Etiology

- Smoking is the main cause of bronchogenic carcinoma. Ninety percent of patients with lung cancer are current or former cigarette smokers. The relative risk of developing lung cancer is increased by about 13-fold in smokers. There is a significant dose-response relationship between the risk of lung cancer and the number of cigarettes smoked per day. The risk is increased 60- to 70-fold for a man smoking two packs a day for 20 years as compared with a nonsmoker. Besides the dose, the form of tobacco smoked is also believed to be important. Those who smoke only pipes or cigars have a lower risk. Bidi smoking is equally harmful. The risk of lung cancer is lower among users of filter than non-filter cigarettes. The risk decreases after stopping smoking. Passive smoking can also increase the risk of lung cancer. The risk may be about twice as compared to non-smokers without such exposure.
- Cigarette smoke contains many carcinogenic polycyclic hydrocarbons like 3, 4 benzopyrine. Squamous cell carcinoma and oat cell carcinoma are common in smokers, whereas adenocarcinoma is common in nonsmokers.
- Other risk factors for developing lung cancer include air pollution, ionising radiation, chromates, metallic iron and iron oxides, arsenic, nickel, beryllium, asbestos, petrochemicals, hematite and mustard gas. Adenocarcinoma can develop in areas of chronic scarring (scar carcinoma).
- Genetic factors like mutations in oncogenes may play an important role in the development of carcinoma. All other risk factors may work by inducing tumor oncogenes.

Pathology

- Squamous cell carcinoma (epidermoid carcinoma) grows relatively slowly and often presents with local symptoms. Small cell carcinoma grows faster and proves rapidly fatal due to early metastasis. Small cell carcinoma is more often central than peripheral. The classical oat cell type is characterised by round or oval nuclei with scanty cytoplasm. Adenocarcinomas commonly present as mid-zone or peripheral mass lesions. Poorly differentiated adenocarcinomas tend to metastasise early and have a poor prognosis. Large cell carcinomas are made up of large malignant cells with abundant cytoplasm.

Clinical Features

- The signs and symptoms of lung cancer are due to local tumor growth, invasion or obstruction of adjacent structures, regional lymph node involvement, metastases and remote effects of tumor products (paraneoplastic syndromes). The patient may be asymptomatic and may be diagnosed incidentally by a chest X-ray.

Symptoms Due to Local Growth

- Central or endobronchial tumor may cause cough, hemoptysis, wheeze and stridor, dyspnea, and post-obstructive pneumonia. Obstruction of airways can produce wheezing, and unilateral wheezing suggests a localized obstruction.
- Peripheral tumor may cause pain from pleural or chest wall involvement, cough, and dyspnea.
- Bronchogenic carcinomas may cavitate and lead to lung abscess formation.

Symptoms Due to Local Invasion

- Local spread of tumor into the mediastinum or involvement of mediastinal lymph nodes may cause tracheal compression, dysphagia due to esophageal compression, hoarseness due to recurrent laryngeal nerve paralysis, elevation of the hemidiaphragm and dyspnea due to phrenic nerve paralysis and Horner's syndrome (enophthalmos, ptosis, miosis, and ipsilateral loss of sweating) due to sympathetic chain compression. Pleural effusion can occur.
- Pancoast syndrome results due to a tumor in the apex or in the superior sulcus of the lung with involvement of the C8 and T1 nerves, cervical sympathetic chain with consequent pain radiating to medial side of arm and forearm, shoulder pain and Horner's syndrome.
- Other problems of local spread include superior vena cava compression, cardiac involvement with resultant malignant pericardial effusion and tamponade, arrhythmia, or cardiac failure.

Symptoms due to Metastases

- Common sites of metastases of lung carcinoma include brain, bone, adrenals, and liver.
- Symptoms are referable to the organ system involved. Brain metastases produce neurologic deficits, bone metastases produce pain and pathologic fractures, bone marrow invasion presents with pancytopenia, liver metastases produces jaundice, and biliary obstruction, spine metastases produces cord compression.

Paraneoplastic Syndromes

- Paraneoplastic syndromes are clinical syndromes due to nonmetastatic systemic effects of a cancer. These syndromes result from substances produced by the tumor, and they occur remotely from the tumor itself.
- Paraneoplastic syndromes occur in approximately 10% of patients with bronchogenic carcinoma and occasionally are the presenting symptom. Paraneoplastic manifestations can be divided into systemic, endocrine, neurologic, cutaneous, hematologic, and renal categories.
- *Systemic manifestations*: Are anorexia, cachexia, weight loss, fever, and suppressed immunity.
- *Endocrine manifestations*: Hypercalcemia and hypophosphatemia may result from production of parathyroid hormone (PTH) or PTH-related peptide by squamous cell carcinoma, SIADH (syndrome of inappropriate secretion of antidiuretic hormone) due to ADH secretion by small cell Ca, and ACTH secretion by small cell carcinoma with resultant electrolyte disturbances.
- *Neurologic*: Eaton-Lambert syndrome and retinal blindness can occur with small cell cancer.
- *Cutaneous*: Itching, icthyosis, herpes zoster.
- *Hematologic*: Anemia, thrombocytosis, disseminated intravascular coagulation (DIC), and leukemoid reactions
- *Rheumatologic*: Hypertrophic pulmonary osteoarthropathy is often associated with clubbing and tenderness over the long bones.
- *Renal*: Hypokalemia, hyponatremia, nephrotic syndrome.
- Paraneoplastic syndrome can often be relieved by treatment of the primary tumor. In many cases the pathophysiology of paraneoplastic syndromes is unknown.

Physical Signs

- Physical examination may reveal clubbing, osteoarthropathy of the wrists and ankles, and lymphadenopathy especially in the supraclavicular regions. RS examination may be normal or show collapse, or consolidation. Pleural effusion may be present. Monophonic wheeze may be heard in localized airway obstruction.

Investigations

Imaging Studies

- Chest X-ray may show an isolated solitary mass lesion. Cavitation or abscess formation may be seen. Doubling time of more than 18 months and presence of calcification strongly suggest a benign diagnosis. Segmental, lobar or massive collapse of the lung may be present. Associated hilar and mediastinal lymphadenopathy may be present. Pleural and pericardial effusion may be present due to invasion of the pleura and pericardium. An elevated diaphragm suggests phrenic nerve involvement. Secondary deposits in the ribs and other bones may be present.
- CT scan of the chest is very useful and helps in differentiating malignant leisons from benign ones. It can also pick up mediastinal lymphadenopathy and metastatic disease in the brain, liver, adrenal, kidney and lymph nodes of the abdomen.
- MRI is particularly useful to detect vertebral, spinal cord, and mediastinal invasion.

Bronchoscopy

- Fibreoptic bronchoscopy is useful to diagnose and obtain biopsy in case of centrally located and endobronchial tumors. When the lesion is endoscopically visualized, diagnosis can be established in more than 90 percent of cases. Bronchoscopy can also reveal paralysed vocal cords and bronchial aspirate and bronchial washings can be obtained to test for malignant cells.

Cytology

- Cytological examination of sputum may show malignant cells. If pleural effusion is present, it should be aspirated and examined for malignant cells. CT-guided FNAC or biopsy from the mass is also helpful for cytological examination.

Mediastinoscopy and Thoracoscopy

- These are sometimes used to take biopsy from lesions and lymph nodes.

Other Diagnostic Techniques

- Biopsy of involved lymph nodes or of a metastatic nodule in the skin, liver, bone or pleura can help in diagnosis.

Management

Surgical Resection

- Surgical resection of the primary tumor and regional lymph nodes is the treatment of choice for NSCLC if the tumor is localized without distant metastases. It is not useful in SCLC.

Radiotherapy

- Radiotherapy is used both for curative purposes as well as for palliative therapy. High-dose radiotherapy can produce equal results as that of surgery in squamous cell carcinoma. It is the treatment of choice for unresectable tumors. It can also be used as adjuvant therapy before or after surgery.

Chemotherapy

- It is being increasingly used in induction (neoadjuvant) therapy in locally advanced, surgically resectable disease. Combined chemotherapy and radiotherapy is useful in small cell carcinoma. Drugs which are useful include mitomycin-C, ifosfamide cisplatin, carboplatin, and etoposide (remember MICE). Chemotherapy is also of great value in malignant pleural effusion and superior mediastinal compression syndrome.

Q. Tumors of the mediastinum.

- *Mediastinum can be divided into four major compartments*: Superior, anterior, middle and posterior.
- The location of each compartment and the tumors that can occur within them are given in Fig. 2.5.

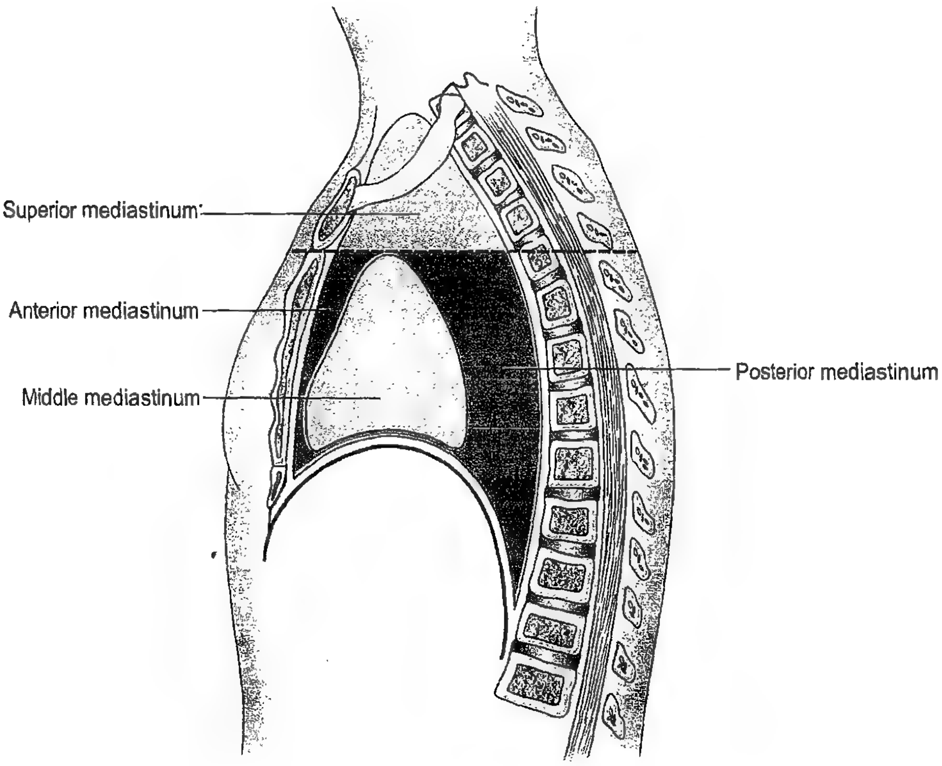

Fig. 2.5: Divisions of mediastinum

2

Table 2.18 Tumors of mediastinum

Divisions of mediastinum	Location	Tumors
Superior mediastinum	Above a line joining the lower border of the 4th thoracic vertebra and the upper end of the sternum	• Retrosternal goiter • Persistent left superior vena cava • Enlarged lymph nodes due to TB • Prominent left subclavian artery • Tumors of thymus • Dermoid cyst • Lymphoma • Aortic aneurysm
Anterior mediastinum	In front of the heart	• Retrosternal goitre • Dermoid cyst • Tumors of thymus • Lymphoma • Enlarged lymph nodes due to TB • Hiatus hernia
Middle mediastinum	Between the anterior and posterior compartments	• Pericardial cyst • Bronchogenic cyst • Aortic aneurysm • Bronchial carcinoma • Lymphoma • Sarcoidosis
Posterior mediastinum	Behind the heart	• Neurogenic tumors • Meningocele • Paravertebral abscess • Esophageal lesion • Diaphragmatic hernia • Aortic aneurysm • Foregut duplication

Clinical Features of Mediastinal Tumors

- Benign tumors can cause pressure effect on trachea or superior vena cava. But most of the time benign tumors are asymptomatic and are diagnosed when chest X-ray is taken for some other reason.
- Malignant tumors can invade and compress adjacent structures. Symptoms and signs depend on the structure compressed which are as follows:
  - *Trachea and bronchi*: Stridor, breathlessness, cough, pulmonary collapse.
  - *Oesophagus*: Dysphagia
  - *Phrenic nerve*: Diaphragmatic paralysis, paradoxical chest movement.
  - *Recurrent laryngeal nerve*: Hoarseness of voice and 'bovine' cough
  - *Sympathetic trunk*: Horner's syndrome
  - *Superior vena cava*: Elevation of JVP, edema of the head and neck and upper limbs. Dilated veins seen on chest wall.
  - *Pericardium*: Pericarditis and/or pericardial effusion.

Investigations

- ***Chest X-ray***: Tumor may be visualized. Mediastinal widening may be present.
- ***CT chest***: This can easily pick up mediastinal growths, the extent of spread and enlarged lymph nodes
- ***Bronchoscopy***: May show intrabronchial lesion which has spread to mediastinum.
- ***Mediastinoscopy***: This can directly visualize the tumors and take biopsy also.

Management

- Treatment depends on the nature of mediastinal pathology. Benign tumors should be removed surgically because they may cause symptoms later.

Q. Miliary mottling in chest X-ray.

- The term miliary mottling refers to innumerable, small 1–2 mm nodules (resembling millet seeds) scattered throughout the lungs. Causes of miliary mottling can be remembered by the pnemonic "Hi STOP MAC"

  Hi—Histoplasmosis, histicytosis X, hemosiderosis
  S—Sarcoidosis
  T—TB
  O—Oil embolism
  P—Pneumoconiosis
  M—Metastasis
  A—Alveolar microlithiasis
  C—Coccidioidomycosis

Q. A patient presents with high-grade fever with chills, cough and chest pain. On examination he has impaired percussion note in the left infrascapular region with a few fine crepitations. What is the most likely diagnosis? How do you investigate and manage this case?

- The most likely diagnosis is pneumonia. Since the patient is coming from the community and not admitted in any hospital prior to development of pneumonia, he is most likely suffering from community acquired pneumonia. For further discussion, see the section on community acquired pneumonia.

Diseases of Cardiovascular System

3

Q. Describe the blood supply and venous drainage of the heart.

- Heart is supplied by mainly two coronary arteries (left main and right coronary arteries), which arise from the aorta just distal to the aortic valve.
- The left main coronary artery divides into the left anterior descending artery (LAD) and left circumflex artery (CX) within 2.5 cm of its origin. LAD runs in the anterior interventricular groove, and the left circumflex artery (CX) runs posteriorly in the atrioventricular groove.
- LAD gives diagonal branches and septal perforation branches which supply the anterior part of the septum, anterior wall and apex of the left ventricle. CX artery supplies the lateral, posterior and inferior segments of the LV.
- The right coronary artery (RCA) runs in the right atrioventricular groove and supplies right atrium, right ventricle and infero-posterior aspects of the left ventricle. A posterior descending artery which is a branch of RCA runs in the posterior interventricular groove and supplies the inferior part of the interventricular septum.

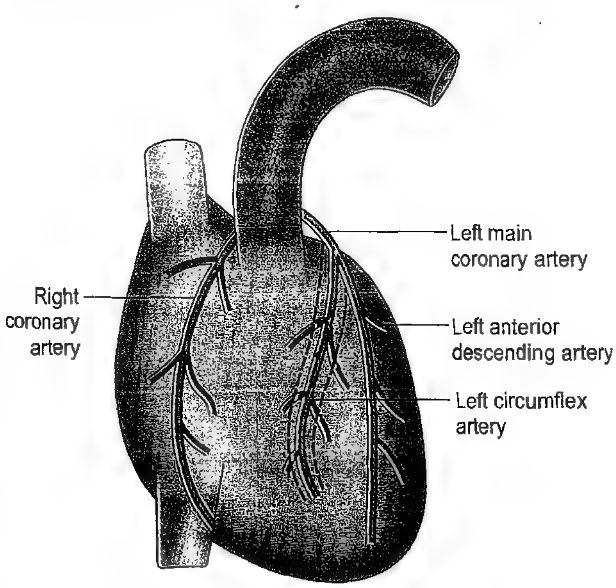

Fig. 3.1: Blood supply of heart

- RCA supplies the sinoatrial (SA) node in about 60% of people, and the atrioventricular (AV) node in about 90%. Proximal occlusion of the RCA therefore can cause sinus bradycardia and AV nodal block. Occlusion of RCA also causes infarction of the right ventricle and inferior part of the left ventricle. Occlusion of the LAD or CX causes infarction of the left ventricular areas supplied by them. Occlusion of the left main coronary artery is usually fatal.
- Venous system of the heart mainly consists of coronary sinus with its draining veins, the anterior right ventricular veins and the Thebesian veins. The coronary sinus lies in the posterior AV groove and drains into the right atrium. Thebesian veins are small veins which drain directly into the cardiac chambers.
- Lymphatics from the heart travel with the coronary vessels and then drain into the thoracic duct.

Q. Nerve supply of the heart.

- The heart is supplied by both sympathetic and parasympathetic fibers.
- Sympathetic fibers arise in the spinal cord and pass through cervical ganglia. The superior, middle and inferior cardiac nerves arise from the respective cervical ganglia and pass through the superficial and deep cardiac plexus to the heart. Sympathetic system supplies muscle fibers in the atria and ventricles and the electrical conducting system. Stimulation of sympathetic fibres produces positive inotropic and chronotropic effect through β_1-adrenoceptors. β_2-adrenoceptors predominate in vascular smooth muscle and mediate vasodilatation.
- Afferent impulses from the heart pass via the spinal cord and the spinothalamic tract into the postero-ventral nucleus of the thalamus.
- The parasympathetic fibers start in the medulla and pass through the right and left vagus nerves. They supply the AV and SA nodes via muscarinic (M2) receptors and have an inhibitory effect. Under resting conditions, vagal inhibitory activity predominates and the heart rate is slow.

Q. Describe briefly the conduction system of the heart.

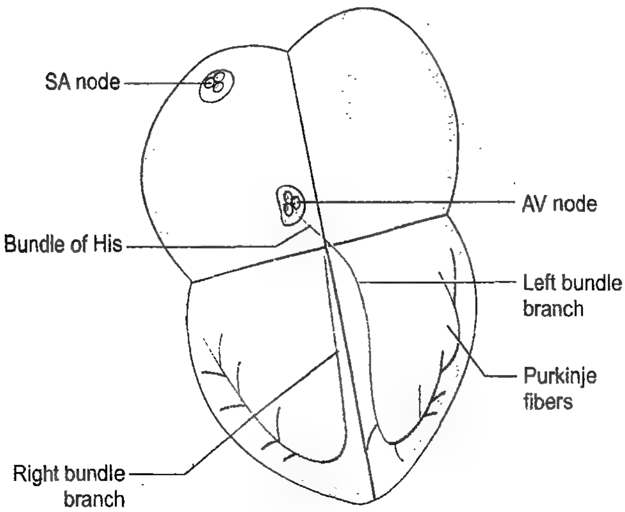

Fig. 3.2: Conduction system of the heart

- The cardiac conduction system is made of specialized conduction tissue and consists of the sinoatrial (SA) node, the AV junctional area, AV node, the bundle of His, bundle branches and terminal Purkinje fibers.
- The SA node is oval in structure, about 1–2 cm long and 0.5 cm thick. It is located at the junction of the right atrium and superior vena cava. SA node is made of special cells and it generates the impulses normally.
- The AV node is situated in the lower right atrium above the insertion of the medial leaflet of the tricuspid valve. It is also ovoid in shape and measures 1 × 3 × 5 mm. It continues as the bundle of His which passes into the ventricular tissue.
- The bundle of His is about 2 cm in length. It divides into right and left bundle branches. The left bundle branch passes down the left side of the interventricular septum. Left bundle branch gives rise to two fascicles known as anterosuperior and posteroinferior fascicles. Right bundle branch is a continuation of bundle of His and runs on the right side of the interventricular septum. Both left and right bundle branches give rise to Purkinje fibers which ultimately supply the ventricles.
- The normal cardiac impulse is generated by SA node. This impulse passes to the AV node through atria. There is a delay in the AV node followed by transmission of the impulse to ventricles through the bundle of His and its branches. The delay in the AV node is responsible for the PR interval on ECG.

Q. Enumerate the symptoms of cardiac disease.

- The major symptoms associated with cardiac disease are:
  - Chest pain (discomfort)
  - Dyspnea
  - Fatigue
  - Edema
  - Palpitations
  - Syncope
  - Cough
  - Cyanosis

Q. What are the causes of chest pain? Discuss the differential diagnosis of chest pain.

Causes of Chest Pain

Cardiac

- Angina
- Myocardial infarction
- Pericarditis

Non-cardiac

- Aortic dissection
- Pulmonary hypertension
- Pulmonary embolism
- Gastroesophageal reflux
- Esophageal spasm
- Peptic ulcer
- Gallbladder disease
- Musculoskeletal disease (costochondritis, rib fracture, muscle pain)
- Pleuritis
- Herpes zoster
- Pneumothorax

Angina

- Felt in the retrosternal region. Usually radiates to left side of neck, jaw, epigastrium, shoulder, and arms. Felt as pressure, burning, squeezing, or heaviness. Usually lasts <20 min. Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin. Prinzmetal's angina may come even at rest. Associated symptoms include sweating, palpitations, dizziness and dyspnea.
- *Main investigations*: ECG will show ST depression and T wave inversion. Cardiac enzymes (CK-MB, troponins) and echocardiogram will be usually normal.

Myocardial Infarction

- Pain is same as angina but more severe and lasts 30 mins or longer. It is not relieved by rest or nitroglycerin. Associated symptoms include dyspnea, sweating, weakness, nausea, and vomiting.

- *Main investigations*: ECG will show ST elevation and pathological Q waves. Cardiac enzymes (CK-MB, troponins) will be elevated. Echocardiogram shows regional wall motion abnormality.

Pericarditis

- Pain is sharp, stabbing and knife-like and lasts for many hours to days. Usually felt over the precordium and may radiate to neck or left shoulder. It is more localized than the pain of myocardial ischemia. It is aggravated by deep breathing and supine position; relieved by sitting up and leaning forward. Auscultation shows pericardial friction rub.
- *Main investigations:* ECG will show ST elevation (with concavity upwards). Echocardiogram may show pericardial effusion or constriction.

Aortic Dissection

- Pain is felt in the anterior chest. It is sudden onset, excruciating, tearing, knife-like and may radiate to back. It usually occurs in people with uncontrolled hypertension or Marfan's syndrome. There may be murmur of aortic insufficiency and pulse or blood pressure asymmetry between the limbs.
- *Main investigations*: Echocardiogram may show the dissection. CT or MR angiography can confirm the diagnosis.

Pulmonary Embolism

- Chest pain is felt in the substernal or over the region of pulmonary infarction. It is of sudden onset and pleuritic (with pulmonary infarction) or angina-like. It lasts minutes to <1 hour and aggravated by breathing. Associated symptoms include dyspnea, tachypnea, tachycardia, hypotension, signs of acute right-sided heart failure, pleural rub, and hemoptysis.
- *Main investigations*: Chest X-ray may show wedge-shaped opacity. ECG may show S1Q3T3 pattern. Echocardiogram may show signs of pulmonary hypertension with dilated right atrium and right ventricle.

Pulmonary Hypertension

- Pain is felt-like pressure in the substernal region. Pain is aggravated by exertion. Associated findings include dyspnea and signs of pulmonary hypertension.
- *Main investigations*: Echocardiogram may show signs of pulmonary hypertension with dilated right atrium and right ventricle.

Gastroesophageal Reflux

- Pain is burning type, felt in epigastric and substernal region and lasts 10 to 60 mins. It is worsened by postprandial recumbency and relieved by antacids.
- *Main investigations*: Upper GI scopy (gastrointestinal scopy) may show reflux esophagitis, regurgitation of stomach contents into the esophagus.

Esophageal Spasm

- Pain is felt as pressure, tightness, or burning sensation in the retrosternal area. It lasts for 2–30 mins and closely mimics angina. Esophageal spasm can be relieved by nitrates adding onto its confusion with angina.
- *Main investigations*: Esophageal manometry can record the increased pressure in the lower part of esophagus due to spasm. Endoscopy is also useful to visualize the inside of esopagus.

Peptic Ulcer

- Pain is burning type, felt in epigastric and substernal region and lasts for a long time. It is relieved by food or antacids and aggravated by spices and alcohol. Associated nausea, vomiting and malena may be present.
- *Main investigations*: Endoscopy will show the ulcer in the stomach or duodenum.

Gallbladder Disease

- Cholecystitis and cholelithiasis can cause epigastric, right upper quadrant, or substernal pain. Pain is felt as burning or pressure sensation and lasts for a long time. It often increases after a meal.
- *Main investigations*: Ultrasound abdomen may show gallstones or features of cholecystitis.

Musculoskeletal Disease

- Like costochondritis can cause chest pain. Pain is aching type and lasts for a variable duration. Pain is aggravated by movement. Localized tenderness may be present.
- *Main investigations*: ECG and other routine investigations will be normal.

Pleuritis

- Pain is felt superficially. It is usually unilateral, and well localized. It is worsened by deep breath and cough. Associated symptoms include cough, fever, crepitations and occasional rub.
- *Main investigations*: Chest X-ray may show underlying pneumonia or pleural thickening or effusion.

Herpes Zoster

- Pain is sharp or burning with dermatomal distribution. Vesicular rash may appear in the dermatomal area.

Pneumothorax

- Pain is sudden onset and lasts for many hours. Pain is usually unilateral on the side of pneumothorax.

Associated features include tracheal shift to opposite side, dyspnea, absent or diminished breath sounds on the side of pneumothorax.

- *Main investigations*: Chest X-ray will show the pneumothorax (air in the pleural space).

Q. Define syncope. Enumerate the causes of syncope. Discuss the approach to a case of syncope.

- Syncope is transient loss of consciousness and postural tone with spontaneous recovery. This definition excludes seizures, coma, shock, or other states of altered consciousness.
- Loss of consciousness happens due to a reduction of blood flow to the reticular activating system of the brainstem. It happen's within 10 seconds of cessation of cerebral blood flow. Patient usually recovers consciousness as soon as he is flat on the ground.
- Though most cases of syncope are benign, there can be serious underlying problems such as cardiac disorders.

Table 3.1 Causes of syncope

Vascular (loss of vascular tone)
- Vascular steal syndromes
- Vasovagal syncope
- Autonomic neuropathy
- Volume depletion
- Carotid sinus hypersensitivity
- Neurally mediated syncope
- Reflex mediated (cough, micturition)
- Drugs (alpha blockers, beta blockers, nitrates)

Cardiac disorders
- Valvular heart diseases (AS, MS)
- Aortic dissection
- Atrial myxoma
- Cardiac tamponade
- Hypertrophic obstructive cardiomyopathy
- Myocardial ischemia, infarction
- Pulmonary embolism
- Pulmonary hypertension
- Arrhythmias

Neurological
- Arnold-Chiari malformation
- Migraine
- Seizure (partial complex, temporal lobe)
- Vertebrobasilar insufficiency
- Transient ischemic attack

Metabolic
- Hyperventilation
- Hypoglycemia
- Hypoxemia

Psychogenic syncope
- Anxiety
- Conversion disorders

Approach to a Case of Syncope

History

- Elicit a detailed history of the event from the patient or bystanders.
- Ask the following questions:
  - Was loss of consciousness complete?
  - Was loss of consciousness with rapid onset and short duration?
  - Was recovery spontaneous, complete, and without sequelae?
  - Was postural tone lost?
- If the answers are yes, syncope is likely; if one, or more answers are negative, other causes of loss of consciousness should be considered.
- ***Precipitating factors***: Include fatigue, sleep or food deprivation, hot weather, alcohol consumption, pain, and strong emotions such as fear or apprehension.
- ***Details of patient activity before the event***: Activity prior to syncope may give a clue to the etiology of symptoms. Syncope may occur at rest; with change of posture; on exertion; after exertion; or with specific situations such as shaving, coughing, voiding, or prolonged standing. Syncope occurring within 2 minutes of standing suggests orthostatic hypotension.
- ***Position of the patient immediately before the syncope occurred***: Syncope while standing indictes orthostatic hypotension. Syncope while seated or lying is more likely to be cardiac.
- ***Symptoms prior to the onset of syncope***: faintness, dizziness, or light-headedness occurs prior to true syncope. Other symptoms, such as vertigo, weakness, diaphoresis, epigastric discomfort, nausea, blurred or faded vision, pallor, or paresthesias, may also occur prior to true syncope. An aura prior to loss of consciousness may suggest seizure. Syncope on exertion, presence of chest pain, dyspnea, and palpitations may suggest cardiac cause. Severe headache, focal neurologic deficits, diplopia, ataxia, or dysarthria prior to the syncopal event suggest neurological cause such as intracranial bleed or vertebrobasilar insufficiency.
- Duration of loss of consciousness (LOC) can indicate the cause. True syncope is associated with LOC lasting for a few seconds to a few minutes. In neurological problems, LOC usually lasts longer, a few minutes to hours.
- Confusion after syncope, tongue bite, urinary and fecal incontinence, convulsive activity, and myalgias indicate siezure as the cause of LOC.
- Obtain drug history, because many drugs cause postural hypotension and syncope. These are calcium channel blockers, alpha blockers, diuretics, etc.

3

- Past history of cardiac disease, sizure disorder, diabetes (hypoglycemia), etc. should be asked. History of pregnancy should be asked because ectopic rupture can cause syncope.

Physical Examination

- *Vital signs*: Fever may point to a precipitant of syncope, such as a urinary tract infection (UTI) or pneumonia. Tachycardia may be an indicator of pulmonary embolism, hypovolemia, tachyarrhythmia, or acute coronary syndrome. Bradycardia may point toward a cardiac conduction defect, or acute coronary syndrome. Postural changes in blood pressure (BP), hypotension, and increased heart rate may point toward an orthostatic cause of syncope. A decrease in systolic BP by 20 mm Hg, a decrease in diastolic BP by 10 mm Hg, or an increase in heart rate by 20 beats per minute (bpm) on standing indicates postural hypotension as the cause of syncope.
- *CVS*: Look for murmurs, signs of cardiac failure such as basal crepitations of lung, presence of S3 and presence of arrhythmias.
- *CNS*: Look for any signs of head injury, pupillary abnormalities, cranial nerve deficits, motor deficits, abnormal deep tendon reflexes, and sensory deficits. Severe neuropathies may correlate with vasodepressor syncope.
- *RS/abdomen*: Look for any abnormalities.

Investigations

- Check blood glucose immediately using glucometer to rule out hypoglycemia. Other tests include complete blood count, serum electrolytes, cardiac enzymes, LFT and renal function tests.
- *ECG*: To rule out acute myocardial infarction or myocardial ischemia, arrhythmias, conduction defects.
- Stool for occult blood to rule out any GI bleed.
- Urine pregnancy test in women to rule out ectopic rupture.
- *Chest radiography* may show evidence of diseases such as pneumonia, heart failure, pulmonary embolism, etc.
- *Computed tomography (CT) of the head*: To rule out any intracranial pathology such as hemorrhage or infarction in patients with neurologic deficits or in patients with head trauma secondary to syncope.
- *CT of the chest and abdomen*: Indicated only in select cases (e.g. suspected aortic dissection, ruptured abdominal aortic aneurysm, or pulmonary embolism [PE]).
- *Echocardiography*: Test of choice for evaluating cardiac causes of syncope such as heart failure, valvular heart diseases, etc.
- *Head-up tilt-table test*: Useful for confirming autonomic dysfunction and postural hypotension causing syncope.
- *Electroencephalography (EEG)*: Indicated if seizure is a likely diagnosis.
- *Stress test*: A cardiac stress test is appropriate for patients in whom cardiac syncope is suspected and who have risk factors for coronary atherosclerosis.

Management

- The treatment of choice for syncope depends on the cause or precipitant of the syncope, as follows:
  - *Situational syncope*: Patient education regarding the condition.
  - *Orthostatic syncope*: Patient education; wearing elastic compression stocking to lower limbs, mineralocorticoids, and other drugs (e.g. midodrine); elimination of drugs associated with hypotension; increasing oral fluid intake.
  - *Cardiac arrhythmic syncope*: Antiarrhythmic drugs or pacemaker placement.
  - *Cardiac mechanical syncope*: Beta blockade; if valvular disease is present, surgical correction.

Q. Write briefly about vasovagal syncope.

- Vasovagal syncope is due to a reduction of venous return to heart due to prolonged standing, hot weather or after meals.
- Decreased venous return leads to underfilling of ventricles which causes Bezold-Jarisch reflex characterized by initial sympathetic activation leading to vigorous ventricular contraction. This stimulates ventricular mechanoreceptors which produces parasympathetic (vagal) activation and sympathetic withdrawal causing bradycardia, vasodilatation or both which leads to syncope.
- Vasovagal syncope can be confirmed by head-up tilt testing, where patient is put on a table which is then tilted to an angle of 70° for up to 45 minutes while the ECG and blood pressure are monitored.
- Treatment is not necessary but in severe cases β-blockers (which inhibit the initial sympathetic activation) or disopyramide (a vagolytic agent) can be used. A dual-chamber pacemaker is useful if the symptoms are predominantly due to bradycardia.

Q. Define cyanosis. Describe the mechanism and causes of cyanosis.

Q. Describe the mechanism of central and peripheral cyanosis. How do you differentiate central from peripheral cyanosis?

Q. Differential cyanosis.

- Cyanosis refers to a bluish discoloration of the skin and mucous membranes due to an increased quantity of reduced hemoglobin or hemoglobin derivatives.
- Cyanosis is seen when reduced hemoglobin concentration in capillary blood is more than 5 g/dl. Cyanosis is also seen when methemoglobin (>1.5%) or sulfhemoglobin (>0.5%) is present in blood.
- It is easily detected on the lips, nail beds, ears, and malar eminences. The degree of cyanosis is modified by the color and thickness of the skin.
- Cyanosis can be divided into two types, central and peripheral.

Mechanism of Cyanosis

- It is the *absolute quantity* rather than the *relative quantity* of reduced hemoglobin which is important in producing cyanosis. Thus, in severe anemia even if the reduced hemoglobin percentage is more; still the absolute quantity is less and hence, may not produce cyanosis. The opposite is true in polycythemia where hemoglobin is increased and can produce cyanosis even with lesser percentages of reduced hemoglobin.
- In central cyanosis SaO_2 is reduced or an abnormal hemoglobin is present, and it affects both skin and mucous membranes. Peripheral cyanosis is due to slowing of peripheral circulation which leads to greater extraction of O_2 from the blood and causes cyanosis. It results from vasoconstriction and diminished peripheral blood flow which occur in cold exposure, shock, congestive failure, and peripheral vascular disease. Peripheral cyanosis usually spares mucous membranes of oral cavity and tongue. In congestive heart failure both peripheral and central cyanosis may coexist.

Table 3.2 Causes of cyanosis

Central cyanosis	Peripheral cyanosis
Decreased FIO_2	• Cardiac failure
• High altitude	• Cold exposure
Lung diseases	• Peripheral vascular disease
• Pneumonia	• Venous obstruction
• COPD	• Raynaud's phenomenon
• Interstitial lung disease	
• Respiratory failure due to any cause	
• Hypoventilation	
• Ventilation perfusion mismatching (pulmonary arteriovenous fistulas)	
Heart diseases	
• Congenital heart diseases with right to left shunt	
• Congestive heart failure with pulmonary edema	
Hemoglobin abnormalities	
• Methemoglobin	
• Sulfhemoglobin	
• Carboxyhemoglobin	

Table 3.3 Differentiation between central and peripheral cyanosis

Feature	Central cyanosis	Peripheral cyanosis
Site	Seen in mucous membranes as well as peripheries	Seen only in peripheries
Evidence of respiratory or cardiovascular disease	Present	Absent
Temperature of peripheries	Warm	Cold
Clubbing of fingers	Usually present and may suggest congenital cyanotic heart disease or pulmonary disease	Absent
Massage or warming of a cyanotic extremity	Cyanosis persists	Cyanosis disappears or decreases
Breathing 100% oxygen	Cyanosis may disappear	Persists
SaO_2	Decreased	Normal

- Cyanosis affecting only lower limbs but not upper limbs is called differential cyanosis. It is seen in patients with patent ductus arteriosus with reversal of shunt.
- Cyanosis of only upper limbs can occur in patent ductus arteriosus with reversal of shunt with transposition of great vessels.

Q. Define palpitation. Enumerate the causes of palpitation. How do you approach a case of palpitation?

- Palpitation is defined as an unpleasant awareness of the forceful, rapid, or irregular beating of the heart.
- Palpitation is a very common and sometimes frightening symptom. It may be due to cardiac or non-cardiac problems. Differentiating cardiac from non-cardiac cause is important because there is a risk of sudden death in those with an underlying cardiac etiology.

Approach to a Patient with Palpitations

- Evaluation of the patient presenting with palpitations begins with a history, physical examination, and 12-lead ECG. Additional testing should be guided by clinical clues.

History

- Figure out what exactly the patient means. A detailed description of the sensation is essential and ask the patient to tap out the palpitation on a table.
- Recurrent but short-lived palpitation or the feeling of missed beat suggests ectopic beats.
- Is the palpitation continuous or intermittent? (Paroxysmal palpitation is suggestive of an arrhythmia. Persistent palpitation is suggestive of a volume overload or a persistent arrhythmia like atrial fibrillation.)
- Is the heart beat regular or irregular? (Irregular palpitation is seen in atrial fibrillation. Regular palpitation is seen in paroxysmal supraventricular tachycardia.)
- Is the onset abrupt? (Abrupt onset seen in arrhythmias, slow onset seen in physiological causes such as exercise).
- How do attacks terminate? (Sudden termination suggests arrhythmia such as PSVT, slow termination suggestive of physiological causes such as exercise.)
- Are there any associated symptoms? For example, chest pain (this suggests myocardial ischemia).
- Light-headedness.
- Polyuria (seen after an attack of supraventricular tachycardia).
- Is there any history suggestive of underlying heart disease such as IHD and valvular heart diseases?
- Is there any extracardiac cause for palpitation (anemia, thyrotoxicosis)?
- A history of panic attacks or anxiety disorder points to a psychiatric cause.
- Is the patient taking any drugs which produce palpitations or arrhythmias?

Examination

- Look for evidence of cardiac problems
- Look for evidence of extracardiac problems such as anemia, thyrotoxicosis, etc.

Table 3.4 Causes of palpitation

Cardiac problems (most common cause)	*Metabolic disorders*	*Physiological*
• Any arrhythmia • Mitral valve prolapse • Valvular heart disease • Ischemic heart disease • Pacemaker • Atrial myxoma • Cardiomyopathy	• Hypoglycemia • Pheochromocytoma	• Stress • Exercise
Psychiatric disease	*High output states*	*Drugs*
• Panic attack • Anxiety	• Anemia • Thyrotoxicosis • Pregnancy • Paget's disease • Fever	• Sympathomimetic agents • Anticholinergic drugs • Beta blocker withdrawal • Cocaine • Amphetamines • Caffeine • Nicotine • Alcohol

Investigations

- ECG to rule out any arrhythmias. Normal resting ECG does not exclude cardiac arrhythmia. Hence, ambulatory ECG monitoring should be considered if arrhythmia is strongly suspected inspite of normal ECG.
- 24-hour holter monitoring is considered if arrhythmia is strongly suspected inspite of normal ECG.
- Echocardiogram to rule out any structural heart disease.
- Exercise stress testing (treadmill testing) is indicated in patients who experience palpitations with exertion.
- Other tests such as hemoglobin, thyroid function tests, 24-hour urinary catecholamine levels, etc. depending on suspicion.

Management

- Treatment depends on the underlying cause.
- Most cases of palpitations are due to an awareness of the normal heart beat, a sinus tachycardia or benign extrasystoles that have been triggered by stress, an intercurrent illness, or the effects of caffeine, alcohol and nicotine. In these situations patient should be reassured.
- Beta blockers may be tried for persistent benign palpitations.

Q. Describe the different types of radial pulse and their clinical importance.

Q. Clinical importance of radial pulse examination.

- Examination of the pulse involves assessment of the following—rate, rhythm, volume, character, condition of the vessel wall, radioradial and radiofemoral delay.
- Other peripheral pulses such as femorals, dorsalis pedis, posterior tibials, subclavians and temporals should be palpated and assessed for any delay or difference in volume. In coarctation of the aorta, the volume of the femoral pulse is lower than radial pulse and also delayed.
- Pulse volume and character are better assessed in the carotid artery. All other parameters can be assessed in the radial pulse.
- The normal carotid and aortic pulse consists of an early percussion wave due to left ventricular ejection, and a second smaller peak tidal wave representing the reflected wave from periphery. However, normally, peripheral pulses such as radial and femoral are felt as single waveform.

Rate

- The normal rate in an adult varies from 60 to 100 per minute. A resting pulse rate below 60 per minute is called bradycardia and above 100 is tachycardia.

Table 3.5 Causes of bradycardia and tachycardia

Bradycardia	Tachycardia
• Athletes	• Anxiety
• During sleep	• Fever
• Hypothyroidism	• Pregnancy
• Vasovagal attack	• Hyperthyroidism
• Heart block	• Cardiac failure
• Sick sinus syndrome	• Tachyarrhythmias
• Hypothermia	• *Drugs:* Salbutamol, aminophylline, vasodilators
• Raised intracranial tension	
• *Drugs*: β blockers, clonidine	

Rhythm

- Normally the pulse is regular except for a slight increase in rate on inspiration and slowing on expiration (sinus arrhythmia).

Irregularly Irregular

- Atrial fibrillation
- Multifocal atrial tachycardia (MAT)
- Frequent extrasystoles

Completely Regular (Loss of Normal Sinus Arrhythmia)

- Autonomic neuropathy

Regularly Irregular

- Sinus arrhythmia
- Pulsus bigeminus, trigeminus
- Partial AV blocks

Volume

- This is the amplitude of pulse wave as judged by the palpating finger. It depends on pulse pressure and is graded as high volume, normal volume, and low volume.

High Volume Pulse (Water Hammer, Collapsing or Corrigan's Pulse)

- Aortic regurgitation
- Patent ductus arteriosus
- Mitral regurgitation
- Ventricular septal defect
- High output states (anemia, hyperthyroidism, beriberi, Paget's disease, arteriovenous fistula)
- Increased stroke volume (complete heart block).

Low Volume Pulse

- Hypovolemia
- Cardiogenic shock
- Tachycardias

- Dilated cardiomyopathy
- Heart failure
- Mitral stenosis
- Aortic stenosis

Varying Volume Pulse (Alternate High and Low Volume Pusles)

- Left ventricular failure

Character of the Pulse

Pulsus Paradoxus

- This is an exaggeration of the normal phenomenon of low volume pulse during inspiration and better amplitude during expiration (normal fall by <10 mm Hg on inspiration). Hence, the name "paradoxus" is a misnomer.
- *Mechanism of pulsus paradoxus*: In normal people, there is reduction of intrathoracic pressure during inspiration, which causes pooling of blood in the right ventricle and pulmonary vasculature, which in turn, results in decreased venous return to left ventricle and low stroke volume.
- Exaggeration of this normal response can be caused by:
  - Restriction of diastolic filling of ventricles (constrictive pericarditis, massive pericardial effusion). Limitation in the diastolic filling of the right atrium and right ventricle during inspiration results in lowering of left ventricular stroke volume.
  - *Right ventricular failure*: This leads to decreased venous return to left ventricle and low left ventricular stroke volume.
  - Increased respiratory effort (severe asthma). During inspiration, owing to enhanced intrathoracic negative pressure, there is pooling of blood in pulmonary veins resulting in lowered left ventricular stroke volume.

Causes of Pulsus Paradoxus

- Constrictive pericarditis
- Cardiac tamponade
- Restrictive cardiomyopathy
- COPD
- Severe asthma
- Tension pneumothorax

Reverse Pulsus Paradoxus

- This refers to inspiratory rise in arterial pressure
- It is seen in hypertrophic cardiomyopathy, positive pressure ventilation and AV dissociation.

Water-Hammer (Collapsing) Pulse or Corrigan's Pulse

- This is characterized by a rapid upstroke, a rapid down stroke and a high volume.
- The rapid upstroke is due to increased stroke volume. Rapid downstroke is due to either diastolic leak back into left ventricle (e.g. aortic regurgitation) or rapid run off to the periphery due to low systemic vascular resistance (e.g. AV fistula).

Causes of Water-Hammer Pulse

- Aortic regurgitation
- Ruptured sinus of Valsalva
- Patent ductus arteriosus
- Mitral regurgitation
- Hyperkinetic circulatory states (anemia, hyperthyroidism, beriberi, Paget's disease, and arteriovenous fistula)

Pulsus Alternans

- This is alternate large volume and low volume pulse. There is a difference of 10–40 mm Hg in systolic pressure between beats.
- It is due to the alternate strong and weak contraction of the left ventricle. When the ventricle contracts poorly there is less stroke volume producing weak pulse. Less stroke volume also leads to increased end diastolic volume in left ventricle which leads to strong contraction and high volume pulse in the next beat according to Starling's law.
- It is seen in cardiac failure.

Pulsus Parvus et Tardus

- This is a slow rising, small volume, well sustained pulse, seen in aortic stenosis.
- Anacrotic pulse is a variant of pulsus parvus in which a notch is palpable between the slowly rising percussion and tidal waves.

Pulsus Bisferiens

- This is a pulse with double-peak during systole. Both peaks are felt during systole. It is seen in combined aortic stenosis and aortic regurgitation. The first peak is due to a quick rising percussion wave and the second peak is due to a delayed tidal wave. The notch is due to aortic regurgitation.

Dicrotic Pulse

- Dicrotic pulse has two palpable peaks, one in systole and other in diastole. First peak during systole is due to the percussion wave, while a second lower peak during diastole is due to accentuated dicrotic wave.
- It is seen in the following conditions:
  - High-grade fever
  - Dilated cardiomyopathy
  - Advanced cardiac failure
  - Cardiac tamponade

Pulsus bigemini or trigemini or quadrigemini

- Here the pulse is regularly irregular and is due to fixed unifocal extrasystoles coming after every normal beat (bigemini) or after every two (trigemini) or three normal beats (quadrigemini), with a pause after the extrasystole.

Condition of arterial wall

- This can be assessed by rolling the radial artery with fingers against the underlying bone. Normally it feels soft and elastic. If the wall is thickened, it feels hard and tortuous.

Radiofemoral and radioradial delay

- Delayed femoral pulse compared to the radial pulse is seen in coarctation of aorta (post-subclavian), aorto-arteritis, or saddle embolus. Radiofemoral delay can be assessed by simultaneous palpation of these two arteries.
- Unequal radial pulses and radioradial delay may be seen in coarctation of aorta (pre-subclavian).
- Unequal carotid pulses could be due to atherosclerotic stenosis in one of the arteries.

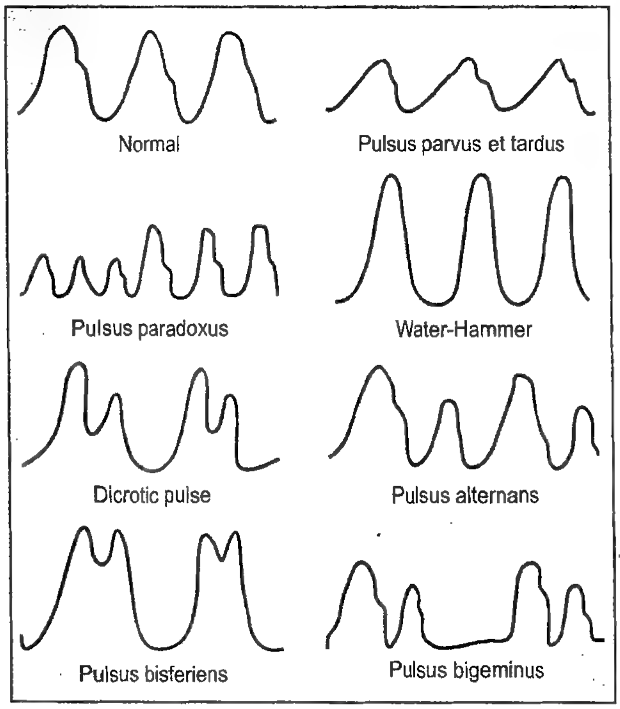

Fig. 3.3: Different types of pulses

Q. Discuss the mechanism of jugular venous pulse.

Q. Describe the importance of examination of JVP. What are the normal wave patterns of JVP and their variations? How do you differentiate JVP from carotid pulse?

Q. Hepatojugular reflux (abdominojugular reflux).

Q. Kussmaul's sign.

- Examination of jugular veins can give valuable clues regarding volume status and right heart events. Since there are no valves between the right atrium and internal jugular veins, right atrial pressure is reflected in these veins.
- The height of JVP is measured as the vertical distance between the top of the venous pulsation and the angle of Louis (sternal angle, where the manubrium meets the sternum). This measurement is normally less than 3 cm. Anything above 3 cm is considered abnormal. The center point of right atrium is about 5 cm below the sternal angle. Hence, if 5 cm is added to the height of JVP measured, we get the actual height of JVP from the midpoint of right atrium to the upper level of JVP which is equal to the jugular venous pressure which is normally less than 8 cm H_2O.
- Some clinicians choose to use the clavicle as a reference point with the patient in seated position. Clavicle is easily located and venous pulsations above that levels are clearly abnormal.

Table 3.6 Causes of elevated JVP

- Right heart failure (cor pulmonale)
- Volume overload
- Tricuspid regurgitation
- Tricuspid stenosis
- Pulmonary HTN
- Pulmonary embolism
- Constrictive pericarditis
- Cardiac tamponade
- Superior vena cava obstruction (non-pulsatile elevation)
- Massive ascites or right-sided pleural effusion

Distinguishing JVP from Carotid Pulse

- Jugular venous pulse should be differentiated from carotid pulse as the later can sometimes be mistaken for the jugular venous pulsation.

Table 3.7 Differences between JVP and carotid pulse

JVP	Carotid pulse
Visible but not palpable	Visible and palpable
Obliterated by pressure at root of neck	Not obliterated
Multiple waveforms	Single waveform
Hepatojugular reflux present	Absent
Definite upper level	No definite upper level
On sitting up upper level of column decreases	No change
Upper level falls on inspiration	No change

Waveforms of JVP and their Mechanism

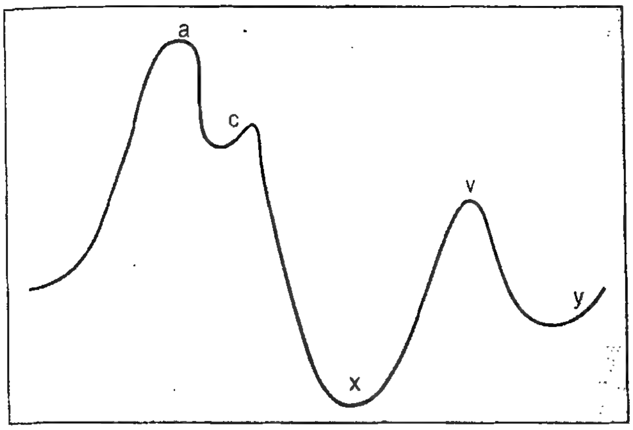

Fig. 3.4: Waveforms of JVP

JVP has 3 positive (a, c, v) and 2 negative waves (x and y)

- *The 'a' wave occurs due to right atrial contraction.* A prominent '*a*' wave is seen in patients with reduced right ventricular (RV) compliance from any cause. A cannon '*a*' wave occurs with A-V dissociation and RA contraction against a closed tricuspid valve. '*a*' wave is absent in atrial fibrillation because there is no coordinated atrial contraction.
- *Next 'x' descent follows and is due to the fall in pressure in the atrium during atrial diastole.* In normal individuals, the *x*' descent is the predominant waveform in the jugular venous pulse.
- The '*x*' descent is interrupted by a *positive 'c' wave which is due to the ventricular systole* pushing the closed tricuspid valve into the right atrium, elevating its pressure.
- *The 'v' wave is due to atrial filling,* and occurs at the end of ventricular systole. Its height depends on RA compliance and the amount of blood in the RA. Normally *v* wave is smaller than the '*a*' wave. In patients with atrial septal defect (ASD), the '*a*' and '*v*' waves may be of equal height.
- *The 'y' descent follows the 'v' wave peak and reflects the fall in RA pressure after tricuspid valve opening.* If there is resistance to ventricular filling in early diastole, the '*y*' descent will be blunted (e.g. pericardial tamponade, tricuspid stenosis). A steep '*y*' descent occurs when the ventricular diastolic filling occurs early and rapidly, as with pericardial constriction. The corresponding auscultatory phenomenon is the pericardial knock.

Kussmaul's Sign

- The normal JVP falls with inspiration. This is due to negative intrathoracic pressure which increases pulmonary vascular compliance.
- Failure to decrease or a rise in JVP pressure with inspiration is known as the Kussmaul's sign.
- Kussmaul's sign is seen in the following conditions:
  - Constrictive pericarditis
  - Restrictive cardiomyopathy
  - Acute severe asthma or COPD
  - Pulmonary embolism
  - RV infarction
  - Right-sided volume overload
  - Advanced systolic failure

Abdominojugular Reflux

- Abdominojugular reflux is performed using firm and consistent pressure over the upper abdomen, preferably the right upper quadrant, for at least 10 seconds.
- Normally there is either no rise or only a transient (2 to 3 seconds) rise in JVP which falls down even if the pressure on the abdomen is continued.
- A sustained rise in JVP until abdominal pressure is released indicates impaired right heart function. This abnormal response is called hepatojugular reflux.
- Patient should not hold his or her breath or perform a Valsalva-like maneuver during the procedure because these can falsely elevate the venous pressure.

Significance

- This can help to confirm that the pulsation is caused by the JVP.
- Abdominojugular reflux indicates a volume-overloaded state and limited compliance of an overdistended or constricted venous system. It is positive in right heart failure. But the normal response is lost in SVC obstruction and Budd-Chiari syndrome.

Q. Discuss the mechanism and variations of first heart sound.

- The first heart sound is mainly due to closure of the mitral and tricuspid valves. It coincides with the R wave on the ECG.
- Normally S1 is louder than S2 at the apex (mitral area). The loudness of the mitral valve closure depends upon 3 things: The degree of valve opening, the force of ventricular contraction shutting the valve, and the integrity of the valve. Think of a slamming door. The amount of its noise will depend on how far open the door is, how hard you slam it, and the integrity of the door.
- S1 has two components: Mitral component (M1) due to mitral valve closure and tricuspid component (T1) due to tricuspid valve closure. Normally these two components are not heard separately as the tricuspid valve closure sound is too faint to hear. However, splitting of first heart sound can be heard sometimes.

Table 3.8 Variations of first heart sound

Loud first heart sound
- Tachycardia
- Short PR interval
- Mitral stenosis
- Tricuspid stenosis
- Left atrial myxoma

Soft first heart sound
- Bradycardia
- Long PR interval
- Mitral regurgitation
- Calcified mitral valve
- Aortic regurgitation (due to premature closure of mitral valve)
- Poor LV function (cardiac failure, cardiomyopathy, myocarditis)
- Decreased conduction of the sound to chest wall (obesity, emphysema, pneumothorax, pericardial effusion)

Varying intensity of first heart sound
- Atrial fibrillation
- Complete atrioventricular block

Splitting of first heart sound
- Right bundle branch block
- Severe mitral stenosis

Q. Discuss the mechanism and variations of second heart sound.

- The second heart sound (S2) is produced by closure of the aortic and pulmonary valves. It has two components; aortic component (A2) due to closure of aortic valve and pulmonary component (P2) due to closure of pulmonary valve.

Table 3.9 Variations of second heart sound

Loud A2
- Hypertension
- Hyperdynamic circulatory states
- Syphilitic aortic regurgitation

Soft A2
- Aortic stenosis

Loud P2
- Pulmonary hypertension
- Pulmonary artery dilatation

Soft P2
- Pulmonary stenosis
- Tetralogy of fallot
- Pulmonary atresia

Wide fixed split
- Atrial septal defect
- Severe pulmonary stenosis
- Severe right ventricular failure

(*contd.*)

Table 3.9 Variations of second heart sound (*contd.*)

Wide mobile split

Delayed activation of right ventricle
- Right bundle branch block
- Ectopic from left ventricle

Prolonged right ventricular systole
- Pulmonary stenosis
- Pulmonary hypertension
- Acute pulmonary embolism

Early aortic closure
- Mitral regurgitation

Reversed splitting

Delayed activation of left ventricle
- Left bundle branch block
- Ectopic from right ventricle

Prolonged left ventricular systole
- Severe hypertension
- Severe aortic stenosis
- Cardiomyopathy
- Acute MI
- Patent ductus arteriosus
- Left ventricular failure

Early pulmonary valve closure
- Tricuspid regurgitation
- WPW syndrome

- Normally A2 comes first and then P2. Both A2 and P2 occur at the end of the T wave on ECG.
- Normally, during inspiration, there is increased venous return to right ventricle and hence pulmonary valve closes late. At the same time due to decreased venous return to left ventricle, aortic valve closes early. This causes physiological splitting of second heart sound during inspiration. During expiration the sound is heard as single. A split S2 is best heard at the pulmonary area since P2 is much softer than A2.

Q. Discuss the mechanism and significance of third heart sound.

- Third heart sound (S3) occurs during the rapid filling phase of ventricular diastole. It is a benign finding in children and young adults. When it is heard in a patient with cardiac disease, it is called a pathologic S3, or ventricular gallop, and usually indicates ventricular dysfunction or atrioventricular (AV) valvular incompetence.
- S3 occurs when the ventricle suddenly reaches its elastic limits and abruptly decelerates the onrushing column of blood. Thus, an S3 can be produced by excessive rapid

3

filling into a ventricle with normal or increased compliance, as with high-output states and MR, or by a normal or less than normal rate of filling into a ventricle with decreased compliance, as in patients with HCM. Likewise, decreased rates of filling into overfilled ventricles with large end-systolic volumes, as seen in patients with LV systolic dysfunction, will produce this sound.

Table 3.10 Causes of S3

Physiological	Pathological
• Children and young adults • Pregnancy	• Cardiac failure • Hyperkinetic circulatory states (anemia, thyrotoxicosis, beriberi) • Mitral or tricuspid regurgitation • Aortic or pulmonary regurgitation

- S3 can be left or right-sided. A left-sided S3 is a low-pitched sound best heard over the LV apex in the left lateral decubitus position. Right-sided S3 (seen in right heart failure) is best heard at the left lower sternal border with the patient supine and on inspiration.

Q. Discuss the mechanism and significance of fourth heart sound.

- A fourth heart sound (S4) occurs due to a forcible atrial contraction against a noncompliant ventricle.
- It can occur in either of the ventricles (right-sided S4 from right ventricle and left-sided S4 from left ventricle). It occurs in the last filling phase of ventricular diastole and is heard just before systole and precedes S1.
- Left-sided S4 is best heard over the apex on expiration with the patient in left lateral position. Right-sided S4 is best heard on inspiration.
- Presence of S4 is always abnormal.

Table 3.11 Causes of S4

Decreased compliance of ventricles due to hypertrophy	Excessively rapid late diastolic filling
• Systemic hypertension • Pulmonary hypertension • Aortic and pulmonary stenosis • Hypertrophic cardiomyopathy • Restrictive cardiomyopathies • Ischemic heart disease	• Acute mitral regurgitation • Acute tricuspid regurgitation • Hyperkinetic states (anemia, thyrotoxicosis)

Q. List the investigations used in the evaluation of cardiac disorders.

Table 3.12 Investigations in cardiac disorders

• Electrocardiography (ECG) – *Resting ECG* – *Exercise (stress) ECG* – *Ambulatory ECG (Holter monitoring)* • Echocardiography (echo) – *Two-dimensional echocardiography* – *Doppler echocardiography* – *Transesophageal echocardiography*	• Chest X-ray • Cardiac catheterization • Computed tomographic (CT) imaging • Magnetic resonance imaging (MRI) • Radionuclide imaging – *Blood pool imaging to assess ventricular function* – *Myocardial perfusion imaging* • Intravascular ultrasound (IVUS)

Q. Electrocardiography (ECG).

Q. Exercise (stress) ECG.

Q. Ambulatory ECG (Holter monitoring).

- ECG is a recording of electrical impulses arising from the heart on the chest wall.
- Normally, cardiac activation starts in the sinoatrial node, goes to atrium, AV node, and then to ventricles through bundle of His and its branches. Each of this stage gives rise to electrical current, which is recorded by the electrodes placed on the chest wall creating the ECG. Though SA node generates impulses, this is not recorded on ECG. Similarly, atrial depolarization produces a little electrical activity and cannot be recorded on ECG. Except these two events, all other events are recorded on the ECG.
- ECG consists of the following waves and segments.

P wave	Due to atrial depolarization
PR interval	Due to the delay in conducting the sinus impulse to ventricles in AV node.
QRS complex	Due to ventricular depolarization
T wave	Ventricular repolarization
QT interval	Represents the total duration of ventricular depolarization and repolarization

Uses of ECG

- To determine the cardiac rhythm and the condition of the conducting tissues
- To diagnose myocardial ischemia and infarction
- To know the effects of some drugs on the heart
- To know the chamber size
- Electrolyte imbalance.

Exercise (Stress) ECG

- Many patients complain of symptoms suggestive of angina on exertion but their resting ECG is normal. Such patients can be made to exercise (walk on a treadmill) and the ECG is recorded continuously during exertion. Such ECG may show ST, T changes proving ischemia or other changes. There are many other indications for stress test.

Indications for Exercise (Stress) ECG

- Evaluation of patients with suspected angina
- Evaluation of stable angina
- Evaluation of functional capacity
- Assessment of prognosis and functional capacity after myocardial infarction
- Assessment of outcome after coronary revascularization, e.g. coronary angioplasty
- To diagnose and evaluate the treatment of exercise-induced arrhythmias.

Procedure

- The commonly used exercise protocol is Bruce protocol. Patient is made to walk on treadmill or bicycle ergometer and 12-lead ECG is continuously recorded during exercise. Blood pressure, heart rate and symptoms are monitored regularly throughout the test.
- Both false positive and false negative tests can occur with stress test. However, in patients with symptoms suggestive of angina, exercise testing has much better sensitivity and specificity, and is clinically very useful.

Contraindications for Stress Test

- Un-stable angina
- Decompensated heart failure
- Severe hypertension
- Uncontrolled cardiac arrhythmias
- Advanced atrioventricular block
- Acute myocarditis or pericarditis
- Severe aortic stenosis
- Severe hypertrophic obstructive cardiomyopathy
- Acute systemic illness (pulmonary embolism, aortic dissection).

Positive Stress Test

- Anginal pain occurs
- ST-T changes suggestive of ischemia (ST segment shifts of >1 mm)
- Fall in BP
- Exercise-induced arrhythmia.

Ambulatory ECG (Holter Monitoring)

- This is a method of recording ECG for prolonged periods of time; these records are analyzed for rhythm and ST-T alterations.
- It is useful for detecting transient episodes of arrhythmia or ischemia, which may not be picked up by a routine 12-lead ECG. ECG analysis wll show whether there were any rhythm disturbances or ST-segment shifts at the time of symptoms.

Technique

- There are many portable devices for ambulatory ECG recording. These devices are compact, battery-operable, can be worn by the patient and permit continuous data recording for 24 hours during daily activities of the patient. The traditional Holter monitor records two ECG channels on a magnetic tape. Event recorders record only the abnormal rhythm whenever they occur. Many of these devices have the facility to transmit ECG recordings to a cardiac center through the telephone.

Q. Echocardiography (echo).

- Echocardiography is nothing but ultrasound of the heart. Images of the heart are obtained by placing the ultrasound transducer on the chest wall.
- It is commonly used because it is noninvasive.

Common Indications for Echocardiography

Assessment of ventricular function
Evaluation of valvular heart diseases
Identification of vegetations in endocarditis
Identification of structural heart disease
Detection of pericardial effusion
Identification of cardiac masses such as myxoma, clots, mural thrombus, etc.

M-mode 2D Echocardiography

- This is a transthoracic ultrasound which records structures in a one-dimensional fashion. By rapid electronic and mechanical scanning of the ultrasonic beam across various cardiac strutures, *2-dimensional (2D) images* can be formed.
- This modality permits evaluation of the size, structure and motion of various cardiac valves and chambers. However, 2D echo does not provide any hemodynamic information (direction of blood flow, etc). Combined conventional and color Doppler echocardiography can assess flow and hemodynamic information also.

Doppler Echocardiography

- Doppler echocardiography is based on the *Doppler effect* described by Christian Doppler. When an ultrasound beam with known frequency is transmitted to the heart, it is reflected by red blood cells. The frequency of the reflected ultrasound waves increases when the red blood cells are moving toward the source of ultrasound and decreases when the red blood cells are moving away.
- The speed and direction of movement of blood across the valves and arteries can be detected by this technique.
- Advanced techniques include three-dimensional echocardiography and intravascular ultrasound.

Uses of Doppler Echocardiography

- It is very useful to evaluate valvular heart diseases. It can detect the severity and direction of blood flow in valvular heart disease such as aortic regurgitation or mitral regurgitation, etc.
- To estimate pressure gradients, e.g. across stenosed aortic valve.

Transesophageal Echocardiography

- Here an ultrasound probe is passed into the esophagus and placed behind the left atrium. It can obtain clear images of cardiac structures especially valves and left atrium.

Uses

- It is useful to pick up vegetations in infective endocarditis which may not be detected by surface echocardiography.
- It is also useful for investigating patients with prosthetic (especially mitral) valve dysfunction, congenital abnormalities (e.g. atrial septal defect), aortic dissection, and systemic embolism.

Q. Uses of computed tomographic (CT) and MRI imaging in the evaluation of cardiovascular disease.

CT Imaging

- CT imaging is most useful for imaging the aorta in suspected aortic dissection. It is also useful to image the chambers of the heart, great vessels, pericardium and surrounding structures.
- Non-invasive imaging of the coronary arteries is possible by using CT angiogram. CT images of the proximal coronary arteries are comparable to conventional coronary angiography. The patency of coronary artery bypass grafts can also be assessed by using CT angiogram.

Magnetic Resonance Imaging (MRI)

- MRI is now considered the gold standard for the assessment of regional and global systolic function, myocardial infarction (MI) and viability, and the assessment of congenital heart disease. It is particularly useful in detecting infiltrative conditions (such as amyloidosis, sarcoidosis) affecting the heart. The right ventricular wall which is difficult to see on echocardiogram is readily visualised on MRI.

Q. Cardiac catheterization.

Q. Coronary angiography (CAG).

Cardiac Catheterization

- Cardiac catheterization is a procedure where a specially designed small catheter is intoduced into the heart through an artery or vein under X-ray guidance. Intoroducing the catheter into the left side of the heart is called left heart catheterization and into the right side is called right heart catheterization.

Technique

- Cardiac catheterization is performed under light sedation and local anesthesia.
- Left heart catheterization is performed through radial, brachial and femoral artery routes. Right heart catheterization is performed through basilic or femoral vein route.

Indications

- To assess coronary artery disease by coronary angiogram (CAG)
- Revascularization procedures such as balloon angioplasty and stenting
- To assess the size and function of the ventricles by ventriculography
- To assess pulmonary artery pressure
- To detect intracardiac shunts by measuring oxygen saturation in different chambers
- To measure intracardiac/intravascular pressures and flow
- Measurement of hemodynamic data in critically sick patients
- For nonsurgical closure of atrial septal defect, ventricular septal defect or patent ductus arteriosus in carefully selected cases
- For temporary/permanent cardiac pacing
- To perform endomyocardial biopsy

Contraindications

- Marked untreated ventricular irritability (risk of ventricular tachycardia/ventricular fibrillation)

- Electrolyte abnormalities and digitalis toxicity
- Marked untreated congestive heart failure
- Uncontrolled hypertension
- Concurrent febrile illness
- Severe renal and/or hepatic impairement
- Severe anemia.

Coronary Angiography (CAG)

Definition

- Coronary angiography is obtaining anatomical details of coronary arteries by injection of radiopaque contrast material into the coronary arteries and thier radiological filming.

Technique

- Technique is described under cardiac catheterization. It involves passing a small specially designed catheter into the aorta and then into the coronary arteries to inject the contrast material. Radial, brachial or femoral routes can be used to enter the aorta.

Indications

- For evaluation of unexplained chest pain with high suspicion of angina
- To establish the site and severity of coronary artery disease in patients with definite angina
- Prior to coronary artery bypass surgery
- To perform balloon angioplasty and stenting
- To perform intracoronary thrombolytic therapy
- To assess the patency of coronary bypass grafts after surgery

Contraindications

- See above under cardiac catheterization

Complications

- Death may occur in cases with advanced coronary disease. However, its incidence is very low (0.1% or less).

Q. Role of radionuclide imaging in the evaluation of cardiac disorders.

- Injecting gamma-emitting radionuclides and picking up the gamma-rays emmited by the heart by gamma camera can be used to assess the ventricular function and myocardial perfusion.
- Left ventricular function can be assessed by injecting the isotope intravenously. Isotope mixes with blood and enters ventricles. Using the gamma camera, the amount of isotope-emitting blood in the heart can be measured in systole and diastole which gives information about ventricular function.
- Myocardial perfusion imaging involves obtaining scintiscans of the myocardium at rest and during stress after the administration of an intravenous radioactive isotope such as technetium-99m tetrofosmin. It can give information about myocardial perfusion and identify areas of ischemia or infarction. Positron emission tomography (PET) scan can give more accurate quantitative information regarding myocardial perfusion, but is available only in a few centers.

Q. Intravascular ultrasound (IVUS).

- IVUS is an invasive procedure, performed along with cardiac catheterization. Here, a miniature ultrasound probe (transducer) on the tip of a coronary catheter is passed into the coronary arteries and detailed images of the interior walls of the arteries are obtained. IVUS shows a cross-section of both the interior, and the arteria wall. Visualization of arterial wall is not possible by conventional angiogram, which shows only the luminal narrowing.

Uses of IVUS

- View the artery—from the inside out, making it possible to evaluate the amount of disease present, how it is distributed, and in some cases, what it is made of.
- Helps in the selection of correct size stents and balloons for angioplasty.
- To confirm accurate stent placement and optimal stent deployment.
- IVUS is useful to assess plaque morphology.
- IVUS can also be used to view the aorta and structure of the artery walls (which can show plaque buildup), find which blood vessel is involved in aortic dissection.

Q. Define heart failure. Describe the etiology, classification, clinical features, investigations and management of heart failure (congestive cardiac failure).

Q. Precipitating causes of heart failure.

Q. Role of ACE inhibitors in the management of heart failure.

Q. Role of beta blockers in the management of heart failure.

Definition

- Heart failure (HF) is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

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- It is a common health problem especially in industrialized countries.

Etiology of Heart Failure

- There are many causes of heart failure. However 5 causes account for most of the cases of heart failure. These are ischemic heart disease (responsible for 70% of cases), cardiomyopathies, congenital, valvular, and hypertensive heart diseases. Following is a list of causes of heart failure.

Table 3.13 Etiology of heart failure

Reduced myocardial contractility
- Myocardial infarction
- Myocardial ischemia
- Myocarditis/cardiomyopathy

Chronic pressure overload
- Hypertension, aortic stenosis (left heart failure)
- Pulmonary hypertension, pulmonary stenosis (right heart failure)

Ventricular inflow obstruction
- Mitral stenosis
- Tricuspid stenosis

Ventricular volume overload
- Mitral regurgitation, aortic regurgitation, ventricular septal defect
- Atrial septal defect

Disorders of rate and rhythm
- Bradyarrhythmias (sinus node dysfunction, conduction abnormalities)
- Tachyarrhythmias (ineffective rhythms, chronic tachycardia)

Diastolic dysfunction
- Constrictive pericarditis
- Restrictive cardiomyopathy
- Left ventricular hypertrophy and fibrosis
- Cardiac tamponade

High output states
- Thyrotoxicosis
- Beriberi
- Chronic anemia
- Systemic arteriovenous shunting
- Paget's disease

Precipitating Causes of Heart Failure

- Precipitating causes make the previously compromised heart fail. These include:
  - *Infection*: Any infection may precipitate HF. Fever, tachycardia, hypoxemia, and the increased metabolic demands due to infection may place additional burden on a compromised heart and lead to heart failure.
  - *Arrhythmias*: Tachyarrhythmias reduce the time available for ventricular filling, and cause ischemic myocardial dysfunction in patients with ischemic heart disease. Atrioventricular dissociation as happens in many brady- and tachyarrhythmias results in the loss of the atrial booster pump mechanism, thereby raising atrial pressure and reduce cardiac output.
  - *Physical, dietary, fluid, environmental, and emotional excesses*: Sudden increase in sodium intake, physical overexertion, excessive environmental heat or humidity, and emotional crises all may precipitate HF.
  - *Discontinuation of drugs*: Such as antihypertensives, diuretics, etc. given for heart failure may precipitate heart failure.
  - *Ingestion of drugs*: Such as NSAIDs can precipitate heart failure.
  - *Myocardial infarction*: A new infarction on a previously compromised heart may precipitate heart falure.
  - *Pulmonary embolism* may result in right heart failure.
  - *Anemia:* In the presence of anemia, the oxygen needs of the metabolizing tissues can be met only by an increase in the cardiac output. An already compromised heart may not be able to tolerate such an increased demand and may fail.
  - *Thyrotoxicosis and pregnancy*: Thyrotoxicosis and pregnancy are high cardiac output states which place increased demand on heart.
  - *Uncontrolled hypertension*: Uncontrolled BP either due to renal problems or discontinuation of anti-hypertensives may result in cardiac decompensation.
  - *Myocarditis*: Rheumatic, viral, and other forms of myocarditis may precipitate HF in patients with or without pre-existing heart disease.
  - *Infective endocarditis*: Valvular damage, anemia, fever, and myocarditis which may occur in infective endocarditis may precipitate HF.

Types

- HF can be classified in many ways. It can be acute or chronic, left-sided or right-sided, high-output or low-output, forward or backward, and systolic or diastolic failure.

Acute Versus Chronic Failure

- In acute failure, there is sudden reduction in cardiac output wich leads to hypotension without peripheral edema, whereas in chronic heart failure, blood pressure is well maintained but there is peripheral edema. Causes of acute heart failure are massive myocardial infarction and valve rupture. Causes of chronic heart failure are valvular heart disease, dilated cardiomyopathy, and systemic hypertension.

Left-sided Versus Right-sided Failure

- In left ventricular failure, there is pulmonary congestion resulting in dyspnea and orthopnea.
- In right-sided failure, systemic congestion leads to raised jugular venous pressure, congestive hepatomegaly, ascites, and lower limb edema.
- Failure of both left and right ventricles is called congestive cardiac failure (CCF) and is seen in long-standing valvular heart disease (aortic and mitral valve), myocarditis, cardiomyopathies, and hypertension.

High Output Versus Low Output Failure

- Examples of high output failure are severe anemia, hyperthyroidism, beriberi, arteriovenous fistulae, pregnancy, and Paget's disease. Here the cardiac output is more than normal.
- Examples of low output failure are ischemic heart disease, hypertension, dilated cardiomyopathy, and valvular and pericardial disease. Here the cardiac output is reduced.

Systolic Versus Diastolic Failure

- In systolic heart failure, heart is not able to pump the blood into arterial system. It happens mainly due to myocardial dysfunction. Examples are myocardial infarction, cardiomyopathy, etc.
- Diastolic failure is due to inability of the ventricle to relax and receive blood, which leads to elevation of ventricular diastolic pressure. Examples are left ventricular hypertrophy, constrictive pericarditis, restrictive cardiomyopathy, etc.
- In most patients with cardiac hypertrophy and dilatation, systolic and diastolic heart failure co-exist.

Pathophysiology

- In the normal ventricle, stroke volume increases over a wide range of end-diastolic volumes (the Frank-Starling effect). In the failing heart with depressed contractility, there is relatively a little increment in systolic function with further increases in left ventricular volume, and the ventricular function curve is shifted downward and flattened. Systolic dysfunction causes pulmonary congestion (left heart failure) or systemic congestion (right heart failure), or both pulmonary and systemic congestion (CCF), effort intolerance, and organ dysfunction.
- The reduction in cardiac output leads to activation of compensatory mechanisms, viz. increased sympathetic activity, stimulation of the renin-angiotensin-aldosterone system (RAAS) and secretion of antidiuretic hormone (ADH). This neurohumoral activation causes tachycardia, peripheral vasoconstriction, sodium and water retention. The result of these compensatory mechanisms is increase in blood pressure (for tissue perfusion) and blood volume (enhancing preload, stroke volume, and cardiac output by the Frank-Starling mechanism). These compensatory mechanisms help to normalize the hemodynamic disturbances to some extent, but increase the myocardial oxygen and energy requirements. In the long run, these compensatory responses perpetuate myocardial damage and worsen heart failure.
- Other compensatory mechanisms are activation of vasodilatory molecules, such as atrial and brain natriuretic peptides (ANP and BNP), prostaglandins (PGE_2 and PGI_2), and nitric oxide (NO), that offset the excessive peripheral vascular vasoconstriction. ANP and BNP cause natriuresis, vasodilation and inhibition of angiotensin II, aldosterone and ADH secretion, thereby reversing some of the harmful effects.

Clinical Features

Symptoms

Dyspnea

- *Exertional dyspnea* is seen in early heart failure. As heart failure advances, dyspnea occurs with progressively less strenuous activity and ultimately it is present even at rest.
- *Orthopnea* is dyspnea in lying down position and is a later manifestation than exertional dyspnea. Orthopnea is due to redistribution of fluid from the abdomen and lower extremities into the chest in lying position, which increases the pulmonary capillary pressure, combined with elevation of the diaphragm.
- *Paroxysmal nocturnal dyspnea (PND)* is sudden onset dyspnea and cough occurring usually 1 to 3 hours after the patient retires. Symptoms usually resolve over 10 to 30 minutes after the patient arises, often gasping for fresh air from an open window. PND happens due to accumulation of excessive blood in the lungs during sleep causing pulmonary edema, depression of the respiratory center and decreased sympathetic activity during sleep. The patient gets up suddenly feeling excessively breathless and choked and lungs for fresh air. He may bring out pink frothy sputum.
- *Acute pulmonary edema* results from transudation of fluid into the alveolar spaces because of acute rise in capillary hydrostatic pressures due to sudden decrease in cardiac function. Patient may present with cough or progressive dyspnea. Wheezing is common due to bronchospasm. If acute pulmonary edema is not treated earlier, patient may begin coughing up pink (or blood-tinged), frothy fluid and become cyanotic and acidotic. Some patients may present with Cheyne-Stokes respiration (periodic

respiration or cyclic respiration) which is characterized by periods of apnea, hypoventilation and hyperventilation.

Fatigue

- This is due to reduced perfusion of skeletal muscles.

Cerebral symptoms

- These are due to reduced cerebral perfusion and include altered mental status, confusion, lack of concentration, memory impairement, headache, anxiety and insomnia.

Abdominal symptoms

- Like nausea, anorexia, and pain abdomen are due to congested gastric mucosa, liver and portal venous system.

Oliguria and nocturia

- Reduced renal perfusion during day causes sodium and water retention and oliguria. Renal perfusion increases at night due to shift of fluid from the extravascular to the intravascular compartment, resulting in increased excretion of sodium and water and nocturia.

New York Heart Association classification of heart failure

- The New York Heart Association (NYHA) classification system is the simplest and most widely used method to gauge symptom severity. The classification system is a well-established predictor of mortality and can be used at diagnosis and to monitor treatment response.

Table 3.14 New York Heart Association (NYHA) functional classification

Functional capacity	Description
I	No limitations of physical activity No heart failure symptoms (fatigue, palpitation, dyspnea)
II	Mild limitation of physical activity Heart failure symptoms with significant exertion; comfortable at rest or with mild activity
III	Marked limitation of physical activity Heart failure symptoms with mild exertion; only comfortable at rest
IV	Discomfort with any activity Heart failure symptoms occur at rest

Physical Signs

Vital signs

- Pulse is fast and of low volume. Pulsus alternans may be seen in LVF
- BP is low in severe heart failure
- Respiratory rate may be high due to pulmonary edema.

General examination

- Patient is dyspneic and orthopneic. Peripheries are cold and may be cyanosed. JVP is usually elevated with positive abdominojugular reflux. Pitting pedal edema may be present. Sacral edema is seen in bedridden patients. In chronic, severe heart failure, weight loss may occur, leading to a syndrome of cardiac cachexia. Cardiac cachexia is due to elevated levels of cytokines.

CVS

- Cardiac enlargement (apex beat shifted down and out) may be seen. S1 may be diminished in intensity. Third and fourth heart sounds are often audible. Pansystolic murmur may be heard due to incompetence of mitral and tricuspid valve due to dilatation of ventricles.

RS

- Tachypnea may be present due to pulmonary edema. Bilateral fine basal crepitations and ronchi may be heard due to pulmonary edema. Sometimes signs of pleural effusion may be present.

Abdomen

- Liver may be enlarged and tender due to congestion. Ascites may be present.

NS

- Confusion, memory disturbances may be seen.

Investigations

- ***Chest X-ray***: The presence of cardiomegaly (a cardiothoracic ratio >0.5 and especially >0.60) is a strong indicator of heart failure. Pulmonary edema may be seen as bilateral batwing hilar haziness, generalized haze (due to interstitial edema), and Kerley's B lines (due to prominent interlobular lymphatics) at the lung base. Bilateral pleural effusion may be seen which is usually more on right side.
- ***Electrocardiogram (ECG)***: It can show cardiac rhythm, identify ischemia, prior or recent MI, and detect evidence of left ventricular hypertrophy. It also shows conduction defects and electrolyte disturbances.
- ***Echocardiography***: Transthoracic echo can confirm the presence of heart failure and also quantify it. It also provides information on left and right ventricular size, regional wall motion abnormality (as an indicator ischemia or infarction), condition of the heart valves, and ventricular hypertrophy. It can also detect left atrial myxoma, and pericardial effusion.
- ***Natriuretic peptide measurements***: Elevated serum levels atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are seen in heart failure.

- *Radionuclide studies*: Provide non-invasive and accurate measurement of wall motion abnormalities, ventricular volume and ejection fraction.
- *Cardiac catheterization*: In heart failure, there is increased end-diastolic ventricular pressure, reduced cardiac output and reduced ventricular ejection fraction. Coronary angiogram can identify the extent of coronary artery disease.

Treatment of Heart Failure

- The ideal approach would be to treat both the underlying and precipitating causes. Correction of underlying cause (e.g. surgical correction of valvular defects) may dramatically improve heart failure. Correction of underlying cause may not always be possible (e.g. old myocardial infarction). Precipitating causes like infections, severe anemia, hyperthyroidism, etc. should be looked for and corrected.

Control of Excessive Fluid

- ***Low salt diet and fluid restriction*** can help in decreasing many of the clinical manifestations of heart failure.
- ***Diuretics***: These agents reduce ECF volume expansion and reduce edema. Many agents are available and almost all are effective in controlling fluid retention. These agents include frusemide, torsemide, thiazides, spironolactone, amiloride, etc. A combination of potassium losing and potassium sparing diuretics will prevent hypokalemia. Hyponatremia can occur due to diuretics and should be watched for.

Prevention of Deterioration of Myocardial Function

- Chronic activation of the renin-angiotensin-aldosterone system (RAAS) and of the adrenergic nervous systems in HF causes ventricular remodeling, further deterioration of cardiac function and/or potentially fatal arrhythmias. Drugs that block these two systems are useful in the management of HF and decrease long-term mortality.
- *Angiotensin-converting enzyme (ACE) inhibitors*: ACE inhibitors slow the maladaptive remodeling of ventricles, and reduce the afterload by causing vasodilatation. ACE inhibitors has been shown to prevent or retard the development of HF in patients with left ventricular dysfunction without HF, enhance exercise tolerance, and reduce long-term mortality and rate of readmission to hospitals. ACE inhibitors inhibit local (tissue) renin-angiotensin systems. ACE inhibitors should be given indefinitely to patients with heart failure. However, ACE inhibition should not be used in hypotensive patients. Examples of ACE inhibitors are captopril, enalapril, lisinopril, ramipril, perindopril, etc.
- *Angiotensin receptor blockers (ARB)*: These agents have similar effects as ACE inhibitors. They are used when patients cannot tolerate ACE inhibitors due to cough, angioneurotic edema, and leukopenia. Examples of ARBs are losartan, telmisartan, olmesartan, etc.
- *Aldosterone antagonist*: The activation of the RAAS in HF increases the levels of angiotensin II and aldosterone. Aldosterone causes Na^+ retention (hence fluid retention), sympathetic activation, myocardial, vascular, and perivascular fibrosis, and vasoconstriction. Spironolactone is an antagonist of aldosterone and when given to heart failure patients on long-term basis reduces mortality and sudden death. Eplerenone is a new, more selective aldosterone inhibitor that can be used instead of spironolactone.
- *Beta-adrenoceptor blockers*: Beta blockers have been shown to improve the symptoms of HF, and to reduce long-term mortality, sudden death, and rehospitalization for HF. They should be given only for patients with moderately severe HF (classes II and III). They should not be given for patients with class IV heart failure, hypotension (systolic pressure <90 mm Hg), severe fluid overload, recent treatment with an intravenous inotropic agent, sinus bradycardia, atrioventricular block, or a bronchospastic condition. Beta blocker should be started after starting ACE inhibitors and continued indefinitely. Examples are atenolol, metoprolol, bisoprolol, and carvedilol.
- *Vasodilators*: Direct vasodilators are helpful in patients with severe heart failure who have systemic vasoconstriction despite ACE inhibitor therapy. Decrease in peripheral resistance enhances cardiac output by decreasing afterload. Sodium nitroprusside, nitroglycerin, hydralazine and nesiritide are vasodilators, which have to be given by continous IV infusion. Hydralazine and isosorbide dinitrate are useful for chronic oral administration.

Enhancement of Myocardial Contractility

- ***Cardiac glycosides (digitalis and digoxin)***: Cardiac glycosides enhance myocardial contractility and hence improve symptoms of heart failure. They inhibit Na^+, K^+-ATPase and increase intracellular [Na^+]. The latter, in turn, increases intracellular [Ca^{2+}] through a Na^+-Ca^{2+} exchange mechanism. The increased Ca^{2+} augments myocardial contraction. Although, digoxin reduces symptoms of HF it does not improve long-term survival. Digoxin is not useful in heart failure due to hypertropnic cardiomyopathy, mitral stenosis, chronic constrictive pericarditis, and diastolic HF.

- *Sympathomimetic amines*: These are dopamine and dobutamine which act on β-adrenergic receptors and improve myocardial contractility. They have to be given by constant intravenous infusion and can be given for several days. They are especially useful in patients with intractable, severe HF, patients with acute myocardial infarction and shock or pulmonary edema or in refractory HF as a "bridge" to cardiac transplantation. Dopamine is useful in heart failure with hypotension since at higher doses it also stimulates β-adrenergic receptors and elevates arterial pressure. Dobutamine is useful in the treatment of acute HF without hypotension since it lowers arterial pressure.
- *Phosphodiesterase inhibitors*: Examples are amrinone and milrinone. Both these drugs exert positive inotropic and vasodilator actions by inhibiting phosphodiesterase III, which increases intracytoplasmic cyclic AMP mediating adrenergic stimulation. These agents are administered by continuous intravenous infusion. Indications are same as dopamine and dobutamine.
- *Ventricular resynchronization*: Intraventricular conduction defects are seen in some patients with heart failure leading to dyssynchrony of cardiac contraction. Right and left ventricles do not contract simultaneously, which impairs cardiac contraction and aggravates HF. "Resynchronization" with a device that has three pacing leads (right atrium, right ventricle, and cardiac vein, which provides left ventricular stimulation) has been shown to improve heart failure symptoms.

Circulatory Assist Devices/Cardiac Transplantation

- When patients do not respond to all the above measures, have class IV heart failure, and are unlikely to survive one year, they should be considered for assisted circulation and/or cardiac transplantation.

Antiarrhythmics

- Premature ventricular contractions and episodes of asymptomatic ventricular tachycardia are common in advanced HF. Sudden death can occur due to ventricular fibrillation. Amiodarone, a class III antiarrhythmic, is the drug of choice for patients with heart failure.
- Implantable automatic, defibrillator (ICD) should be considered for patients who have been resuscitated from sudden death, and those with syncope or presyncope due to ventricular arrhythmias.

Anticoagulants

- Routine use of anticoagulants (e.g. warfarin) is not recommended in patients with heart failure in sinus rhythm who do not have demonstrated left ventricular thrombus. Anticoagulation is recommended if there is atrial fibrillation or a previous thromboembolic event.

Treatment of Diastolic Heart Failure

- The underlying cause such as ventricular hypertrophy, fibrosis, or ischemia should be treated. Dietary Na^+ restriction and diuretics are useful to reduce pulmonary and/or systemic venous congestion.

Non-pharmacological Measures

- *Rest:* Rest reduces the demand on the heart. Adequate rest reduces venous pressure and pulmonary congestion. Absolute bed rest is not required even for patients with severe HF.
- *Diet:* The diet should provide adequate calories to maintain ideal weight. Obese patients should have a low-calorie diet. Oils and fats should be cut down. The sodium intake should not exceed 6 g of salt per day. Potassium-rich foods are advised for those receiving diuretics.

Q. Brain natriuretic peptide (BNP).

- BNP is a peptide hormone that is released primarily by ventricles in response to volume expansion. BNP is so-called because it was initially identified in the brain.
- The level BNP is increased in heart failure, as ventricular cells secrete BNP in response to the high ventricular filling pressures. Ventricles also secrete atrial natriuretic peptide (ANP), but measurement of BNP is more helpful than ANP in the diagnosis of heart failure. Clinical experience with BNP is much greater than ANP.
- BNP has diuretic, natriuretic, and hypotensive effects. It also inhibits the renin-angiotensin system, endothelin secretion, and systemic and renal sympathetic activity. Hence, BNP counteracts the effects of norepinephrine, endothelin, and angiotensin II, limiting the degree of vasoconstriction and sodium retention. BNP may also protect against collagen accumulation and the pathologic remodeling that contributes to progressive HF.

Uses of BNP

- To differentiate dyspnea due to heart failure from other causes. Most dyspneic patients with HF have values above 400 pg/ml, while values below 100 pg/ml have a very high negative predictive value for HF as a cause of dyspnea.
- *Monitoring treatment of heart failure*: The plasma concentrations of BNP fall after effective treatment of HF and can be used to titrate treatment.
- *Prognosis of HF*: Higher the BNP, poorer the prognosis.

Q. Enumerate the clinical features of left heart failure.

Table 3.15 Clinical features of left heart failure

Symptoms	Signs
• Dyspnea, orthopnea, PND • Nocturia • Palpitations	• Pallor • Sweating • Pulsus alternans • Narrow pulse pressure • Left ventricular S3 and S4 gallop • Bilateral basal lung crepitations

Q. Enumerate the clinical features of right heart failure.

Table 3.16 Clinical features of right heart failure

Symptoms	Signs
• Anorexia, nausea, vomiting (due to gastric mucosal congestion) • Right hypochondrial pain (due to liver congestion)	• Peripheral edema • Raised JVP • Ascites, pleural effusion • Right ventricular S3 and S4 gallop

Q. What is refractory heart failure? Discuss the management of refractory heart failure.

- When heart failure does not respond to conventional treatment, it is considered refractory heart failure.

Table 3.17 Causes of refractory heart failure

• Severe anemia • Active rheumatic carditis • Hypertension • Hyperthyroidism • Infective endocarditis • Constrictive pericarditis • Pericardial effusion	• Cirrhosis of liver • Nephrotic syndrome • Pulmonary embolism • Chronic alcoholism • Vitamin B deficiency • Electrolyte and acid–base disturbances • Surgically treatable lesions, e.g. mitral stenosis, aortic stenosis, atrial tumors

Treatment

- Correct the underlying cause.
- Intravenous vasodilator (sodium nitroprusside) along with dobutamine or dopamine infusion may help temporarily.
- Intravenous infusion of amrinone and milrinone may help temporarily.
- Intravenous infusion of nesiritide (recombinant B-type natriuretic peptide) has vasodilator and natriuretic action. It can provide sustained reduction in filling pressures.
- End-stage refractory heart failure may respond to intra-aortic balloon pump, left ventricular assist devices, and ventricular resynchronization therapy.
- For long-term benefit, cardiac transplantation is the choice.

Q. Digoxin.

Q. Manifestations and management of digoxin overdosage.

- Digoxin is a purified glycoside from *Digitalis lanata*. It has been used for more than 200 years in the treatment of heart failure.

Actions

- It inhibits Na-K-ATPase pump in myocardial cells. Increased intracellular sodium promotes sodium-calcium exchange, leading to a rise in the intracellular calcium concentration. This results in improved myocardial contractility.
- Digoxin also exerts antiadrenergic action in patients with HF by inhibiting sympathetic outflow and augmenting parasympathetic tone thereby causing vasodilatation and reduction of afterload.
- It prolongs the refractory period of AV node by increasing parasymphathetic outflow leading to slowing of ventricular rate.

Pharmacokinetics

- Digoxin has oral bioavailability of about 80%.
- Higher concentration is seen in heart than plasma. It is highly protein bound and hence, it is not effectively removed by hemodialysis in case of toxicity.
- Its half life is 1.6 days and the effect lasts 24–36 hours after the last dose.
- It is mainly excreted by the kidneys and small amount in the stools.

Uses of Digoxin

- *Severe heart failure in sinus rhythm*: It improves the symptoms of heart failure but does not provide any mortality benefit.
- *Arrhythmias*: Such as atrial fibrillation with fast ventricular rate for ventricular rate control.

Dosage and Route of Administration

- *Loading dose*: An initial dose of 0.5 mg of digoxin is given IV or orally, followed by over several minutes, followed by 0.25 mg every 6 hours until digitalization is achieved.
- Maintenance dose: 0.125 to 0.25 mg daily orally. Maintenance dose should be reduced in renal failure.

Overdosage (Toxicity)

Clinical Features

- Symptoms of digoxin toxicity are mostly nonspecific, and include fatigue, blurred vision, disturbed color perception, anorexia, nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, confusion, delirium, and occasionally hallucinations.
- Cardiovascular effects include bradycardia, atrioventricular block with or without concomitant supraventricular tachyarrhythmia, and ventricular tachyarrhythmias. Hyperkalemia also occurs in acute poisoning.

Treatment

- *Digoxin*—specific antibodies are used for hemodynamically significant arrhythmias.
- Other supportive measures include atropine, dopamine, epinephrine, phenytoin, and external cardiac pacing for bradyarrhythmias and magnesium, lidocaine, phenytoin, and bretylium for ventricular tachyarrhythmias.

Q. Cor pulmonale.

Q. Discuss the etiology, pathogenesis, clinical features, investigations, and management of chronic cor pulmonale.

- Cor pulmonale is defined as an alteration in the structure and function of the right ventricle due to respiratory system disease.
- Pulmonary hypertension is the link between respiratory system disease and cor pulmonale. Respiratory diseases cause pulmonary hypertension, which in turn, causes cor pulmonale. In cor pulmonale, there is enlargement of the right ventricle (RV) with or without failure.
- Secondary to abnormalities of the lungs, thorax, pulmonary ventilation, or circulation.
- Cor pulmonale can be acute or chronic. Acute cor pulmonale develops suddenly and is seen in massive pulmonary embolism and ARDS. Chronic cor pulmonale develops slowly.

Etiology of Cor Pulmonale

Table 3.18 Etiology of cor pulmonale

Mechanism of cor pulmonale	Causes
Persistent vasoconstriction	• High-altitude dwellers • Hypoventilation syndromes (pickwickian syndrome, myasthenia gravis) • Chest deformities (kyphoscoliosis)
Loss of cross-sectional area of the vascular bed	• COPD (emphysema) • Lung resection • Interstitial lung disease • Bronchiectasis • Cystic fibrosis
Obstruction of large vessels	• Extrinsic compression of pulmonary veins • Fibrosing mediastinitis • Adenopathy/tumors • Pulmonary embolism
Chronically increased blood flow	• Eisenmenger's syndrome
Vascular remodeling	• Primary pulmonary hypertension • Secondary pulmonary hypertension • Collagen vascular diseases • Cystic fibrosis

Pathogenesis

- All the causes of cor pulmonale affect the right heart by producing pulmonary hypertension. Pulmonary hypertension places extra load on right heart and makes it dilate and fail.
- Hypoxia is a strong vasoconstrictor of the pulmonary artery and its branches. Other factors leading to pulmonary hypertension are reduction of the pulmonary vascular bed by fibrotic and thrombotic obliteration of the capillaries and compression of pulmonary capillaries by high intra-alveolar pressures, when there is air trapping.

Clinical Features

- Patients usually have symptoms related to the underlying pulmonary disorder like cough, exertional dyspnea, wheezing, easy fatigability, and weakness. In acute cor pulmonale due to pulmonary embolism, there may be signs of DVT.
- With the onset of RV failure, peripheral edema and right upper quadrant pain (due to congested liver) appear.
- Examination may reveal cyanosis, clubbing, raised JVP, signs of right ventricular hypertrophy (RV heave, epigastric pulsations, loud P2) an enlarged, and tender liver and dependent edema.

Investigations

Chest X-ray

- Chest X-ray may show the underlying lung disease, enlarged RV and dilated pulmonary artery.

ECG

- ECG may show signs of right ventricular hypertrophy such as right axis deviation, peaked P waves, and deep S waves in lead V1.

Echocardiogram

- Echo shows normal LV size and function but RV and RA dilation.

Other Tests

- Tests to diagnose the underlying cause of cor pulmonale are pulmonary function tests (for COPD), perfusion lung scans and multislice CT (to exclude pulmonary emboli) and lung biopsy to rule out interstitial lung disease. Catheterization of the right heart can confirm the diagnosis of cor pulmonale by demonstrating increased RV and RA pressures.

Treatment

- Underlying pulmonary disease responsible for cor pulmonale should be treated. Oxygen supplementation, salt and fluid restriction, and diuretics are helpful in managing right heart failure.

Q. Acute pulmonary edema.

- Acute pulmonary edema (APO) refers to the rapid buildup of fluid in the alveoli and lung interstitium that has extravasated out of the pulmonary circulation.
- As the fluid accumulates, it impairs gas exchange and decreases lung compliance, producing dyspnea and hypoxia. Pulmonary edema can be broadly divided into two types: Cardiogenic and non-cardiogenic pulmonary edemas.
- ***Cardiogenic pulmonary edema (synonyms: acute left heart failure, cardiac asthma):*** This form of pulmonary edema occurs when left ventricular failure occurs, so that blood returning to the left atrium exceeds that leaving the left ventricle (LV). As a result, pulmonary venous pressure increases, causing the capillary hydrostatic pressure in the lungs to exceed the oncotic pressure of the blood, leading to filtration of fluid out of the capillaries.
- ***Non-cardiogenic pulmonary edema:*** Pathological processes acting either directly or indirectly on the pulmonary vascular permeability cause this form of pulmonary edema. Transudation of fluid from pulmonary capillaries into the alveoli results in pulmonary edema. Transudation of fluid from pulmonary capillaries into the alveolar interstitial space causes interstitial pulmonary edema, which precedes the development of alveolar pulmonary edema.

Causes of Pulmonary Edema

Cardiogenic

- Acute myocardial infarction or severe ischemia
- Exacerbation of chronic heart failure
- Acute volume overload of the LV (e.g. valvular regurgitation)
- Mitral stenosis
- Atrial fibrillation
- Accelerated hypertension
- Infective endocarditis.

Non-cardiogenic

- High output states (anemia, thyrotoxicosis)
- ARDS (sepsis, pancreatitis, burns, polytrauma)
- Eclampsia
- Immersion/submersion
- Toxic inhalation
- High altitudes (HAPE) and decompression illness
- Head injury/intracranial hemorrhage.

Clinical Features

- Patient presents with severe dyspnea, orthopnea, PND, pink frothy sputum, and excessive sweating.
- Examination shows cyanosis, bilateral basal crepitations, and diffuse rhonchi.
- There may be tachycardia and S3 gallop in LVF.
- In addition, there may be findings of underlying disease.

Investigations

- *Chest X-ray* shows increased interstitial markings, and butterfly pattern of distribution of alveolar edema. Kerley's B lines may be seen due to thick and tense lymphatics. Cardiomegaly may be present.
- *ECG* may show evidence of ischemia, infarction, and arrhythmias.
- *Echocardiography* shows low ejection fraction and elevated atrial pressures in cardiogenic pulmonary edema.
- *Pulmonary capillary wedge pressure (PCWP)* is elevated in cardiogenic pulmonary edema usually above 25 mm Hg. In noncardiogenic pulmonary edema, the wedge pressure may be normal or even low.

Treatment

Cardiogenic Pulmonary Edema

General measures

- Patient should be put in sitting position with legs hanging down the side of the bed. This position decreases venous return to heart and improves pulmonary edema. High flow oxygen is given through face mask. Noninvasive or invasive ventilatory support may be required in severe respiratory distress.

Morphine

- Morphine is very effective in cardiogenic pulmonary edema. It acts by increasing venous capacitance, lowering left atrial pressure. It also relieves anxiety thus increasing the efficiency of ventilation. The initial dosage is 2–8 mg intravenously which can be repeated after 2–4 hours.

Diuretics

- Intravenous diuretics (furosemide, 40 mg, or torsemide 20 mg—or higher doses) decrease fluid overload and preload. Benefit is seen even before the onset of diuresis due to venodilation.

Nitroprusside, nitroglycerin, and nesiritide

- All these drugs decrease arterial resistance and increase venous capacitance thus decreasing pulmonary blood flow and pulmonary venous pressures. Sublingual nitroglycerin or isosorbide dinitrate, topical nitroglycerin, or intravenous nitrates will decrease dyspnea rapidly prior to the onset of diuresis.

Inotropic drugs

- Like dopamine, dobutamine, amrinone and milrinone may improve cardiac output and decrease pulmonary edema.

Non-cardiogenic Pulmonary Edema

- Treat the underlying cause

Q. What is infective endocarditis? Discuss the etiology, types, pathogenesis, clinical features, and management of infective endocarditis. Add a note on infective endocarditis prophylaxis.

Q. Duke criteria.

- Infective endocarditis (IE) is defined as an infection of the endocardial surface of the heart.
- It may involve heart valve (native or prosthetic), the lining of a cardiac chamber or blood vessel, a congenital anomaly (e.g. septal defect) or an intracardiac device.
- The causative organism is usually a bacterium, but may be a Rickettsia, Chlamydia or fungus.
- It is characterized pathologically by the presence of vegetation, which is a mass of platelets, fibrin, microorganisms, and inflammatory cells.

Types

- Endocarditis may be classified according to the temporal evolution of disease as acute and subacute endocarditis.
- *Acute endocarditis* is a serious illness with high-grade fever. It rapidly damages cardiac structures, hematogenously seeds extracardiac sites, and if untreated, may result in death within weeks.
- *Subacute endocarditis* follows an indolent course, causes structural cardiac damage only slowly, if at all, and rarely causes metastatic infection.
- *Postoperative endocarditis* usually occurs in patients after heart valve surgery. Any unexplained fever in such patients should be investigated for possible endocarditis. The infection usually affects the valve ring and may resemble subacute or acute endocarditis, depending on the virulence of the organism. Repeat surgery may be required and morbidity and mortality are high. Microorganisms are similar to acute and subacute endocarditis. In the first few weeks after surgery, coagulase-negative Staphylococcus is the commonest cause.

Etiology

Table 3.19 Etiology of endocarditis

Acute endocarditis	Subacute endocarditis
• Staphylococcus	• *Streptococcus viridans*
• Pseudomonas	• *Streptococcus milleri*
• *Streptococcus pneumoniae*	• *Streptococcus bovis*
• Candida	• *Enterococcus fecalis*
• *Neisseria gonorrhoeae*	• *Staphylococcus aureus*
	• HACEK group

- The causative organism can be bacteria, Rickettsia, Chlamydia or fungus.
- However, most cases of infective endocarditis are caused by a small number of bacterial species. These include *Streptococcus viridans*, staphylococci, and HACEK organisms (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella) originating respectively from oral cavity, skin, and upper respiratory tract. *Streptococcus bovis* originates from GIT, and enterococci from the genitourinary tract.
- Nosocomial endocarditis is due to bacteremia arising from IV cannulas and urinary tract infections. Candida species is the commonest fungal endocarditis.

- Prosthetic valve endocarditis occurring within 2 months of valve replacement is usually due to intraoperative contamination of the prosthesis or a bacteremic postoperative complication. It can be delayed up to 12 months. Common organisms are coagulase-negative staphylococci, *S. aureus*, facultative gram-negative bacilli, diphtheroids, and fungi. Prosthetic valve endocarditis occurring >12 months after surgery are due to the same organisms causing native valve endocarditis.
- Endocarditis occurring in IV drug abusers is due to *S. aureus* strains, and involves tricuspid valve. Polymicrobial endocarditis is common in IV drug addicts.
- About 5 to 15% of patients with endocarditis have negative blood cultures. Some of these culture negative cases are due to prior antibiotic exposure. Remaining culture negative cases are due to fastidious organisms, such as pyridoxal-requiring streptococci (now designated abiotrophia species), HACEK organisms, *Bartonella henselae*, or *Bartonella quintana*.

Pathogenesis

- Organisms that cause endocarditis usually enter the bloodstream from mucosal surfaces, skin, or sites of focal infection.
- Normal endocardium is resistant to infection and to thrombus formation. Endocardial injury (e.g. at the site of impact of high-velocity jets or on the low-pressure side of a cardiac structural lesion, mitral regurgitation, aortic stenosis, aortic regurgitation, ventricular septal defects, and complex congenital heart disease) predisposes to infection or to development of platelet-fibrin thrombus. This platelet-fibrin thrombus without microorganisms is called nonbacterial thrombotic endocarditis (NBTE) which can subsequently get infected by bacteria during transient bacteremia.
- NBTE can also occur in hypercoagulable states like malignancy and chronic diseases (marantic endocarditis), systemic lupus erythematosus and antiphospholipid antibody syndrome.
- Microorganisms adhere to thrombi but more virulent bacteria (e.g. *S. aureus*) can adhere directly to intact endothelium or exposed subendothelial tissue. If the organisms cannot be removed by defence mechanism, the organisms proliferate and induce a procoagulant state at the site by eliciting tissue factor from adherent monocytes.
- Tissue factor leads to fibrin deposition, and along with platelet aggregation and microorganisms, forms an infected mass called vegetation. Vegetations have three layers; an inner layer of RBC, WBC and platelets, a middle layer of bacteria and an outer layer of fibrin. In the absence of host defenses, organisms enmeshed in vegetation proliferate to form dense microcolonies. Organisms deep in vegetations are relatively resistant to killing by antimicrobial agents. Proliferating surface organisms are shed into the bloodstream continuously some of which are cleared by the reticuloendothelial system and others are distributed to all parts of the body.
- Release of cytokines by inflammatory cells causes constitutional symptoms like fever, malaise.
- Damage to intracardiac structures leads to valvular incompetence and other manifestations.
- Embolization of vegetation fragments leads to infection or infarction of remote tissues.

Clinical Manifestations

- The clinical presentation can vary from acute to subacute presentations. Usually the causative microorganism is responsible for the temporal course of endocarditis.

Systemic Manifestations

- In patients with subacute endocarditis, fever is typically low-grade and rarely exceeds 103°F. In acute endocarditis fever is usually between 103 and 104°F. Fever may be blunted or absent in elderly, debilitated and those with cardiac or renal failure.
- Drenching night sweats, arthralgias, myalgias (especially in the lower part of the back and thighs), and weight loss may accompany fever.

Cardiac Manifestations

- Regurgitant murmurs may occur due to destroyed or distorted valve and its supporting structures. Stenotic murmurs can occur due to large vegetations. Murmurs may be absent initially and appear later.
- Valve ring abscess may occur due to local extension of the infection from the valve ring. Valve ring abscesses can cause persistent fever and heart block due to destroyed conduction pathways in the area of the atrioventricular node and bundle of His. Valve ring abscess may burrow into pericardium causing pericarditis or hemopericardium. It can also lead to shunts between cardiac chambers or between the heart and aorta.
- Myocardial infarction may result from coronary artery embolization.
- Myocardial abscess may occur as a consequence of bacteremia.
- Diffuse myocarditis can occur and is probably due to immune complex vasculitis.
- Congestive cardiac failure develops in 30 to 40% of patients due to valvular dysfunction and occasionally due to endocarditis-associated myocarditis or an intracardiac fistula. CHF occurs more frequently with left-sided than right-sided endocarditis and with aortic more than mitral involvement.

Embolic Manifestations

- *Embolic events* result in infarction of numerous organs, such as the lung in right-sided endocarditis or the brain, spleen, or kidneys in left-sided endocarditis. Following are the manifestations of embolic events. Most emboli occur before or within the first few days after initiation of antibiotic therapy.
- Cutaneous embolism—produces Janeway's lesions. These are hemorrhagic, nonpainful macules most commonly found on the palms and soles.
- Nails—splinter hemorrhages. These are nonblanching, linear, brownish-red lesions in the nailbeds perpendicular to the direction of growth of the nail; they may also be seen as a result of local trauma.
- Peripheral arteries—claudication, absent pulses and gangrene.
- CNS—seizures, stroke, loss of vision.
- Kidneys—loin pain, hematuria and renal failure
- Lungs—pulmonary infarction, hemoptysis, pleurisy and pleural effusion.
- Septic emboli—suppurative complications such as abscesses, septic infarcts, and infected mycotic aneurysms. Mycotic aneurysms are focal dilations of arteries occurring at points in the artery wall that have been weakened by infection in the vasa vasorum or where septic emboli have lodged. Mycotic aneurysms usually develop at arterial bifurcations, e.g. in the middle cerebral, splenic, superior mesenteric, pulmonary, coronary, and extremity arteries.

Immunologic Phenomena

- Glomerulonephritis, sterile meningitis, and polyarthritis.
- Mucocutaneous petechiae.
- Roth's spots—circular retinal hemorrhages with white central spot.
- Osler's nodes—painful tender nodules in the pulps of fingers.
- Hepatosplenomegaly may develop with prolonged illness.

Diagnosis

The Duke Criteria

- Duke criteria are based on clinical, laboratory, and echocardiographic findings. It is highly sensitive and specific for the diagnosis of infective endocarditis. Presence of two major criteria, or one major and three minor criteria, or five minor criteria is required to make a clinical diagnosis of definite endocarditis. If one major and one minor criteria or three minor criteria are present then it is called possible infective endocarditis.

Table 3.20 Duke criteria

Major criteria

1. **Blood cultures positive**
   - Typical organism from two cultures (viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*) OR
   - Blood cultures persistently positive for one of these organisms, from cultures drawn more than 12 hours apart OR
   - Single positive blood culture for *Coxiella brunetti* or IgG antibody titer greater than 1:800
2. **Evidence of endocardial involvement**
   - Positive echocardiographic findings of vegetations
   - New valvular regurgitation

Minor criteria

1. **Fever ≥38.0°C (≥100.4°F)**
2. **Immunologic phenomena:** Glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
3. **Vascular phenomena:** Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. **Echocardiogram results consistent with IE but not meeting major echocardiographic criteria**
5. **Predisposition:** Predisposing heart condition or injection drug use
6. **Microbiological evidence (positive blood culture but not meeting major criterion)**

Pnemonic to remember above criteria is ***"BE FIVE PM"***. ***B:*** *Blood culture positivity,* ***E:*** *Endocardial involvement by ECHO;* ***FIVE PM*** *indicates first letter of each minor criteria.*

- The diagnostic criteria attach significance to the species of organism isolated from blood cultures. To fulfill a major criterion, the isolation of an organism that causes both endocarditis and bacteremia in the absence of endocarditis (e.g. *S. aureus*, enterococci) must take place repeatedly (i.e. persistent bacteremia) and in the absence of a primary focus of infection.
- Organisms that rarely cause endocarditis but commonly contaminate blood cultures (e.g. diphtheroids, coagulase-negative species) must be isolated repeatedly if their isolation is to serve as a major criterion.

Blood Cultures

- Isolation of the causative microorganism from blood cultures is important not only for diagnosis but also for treatment. In the absence of prior antibiotic therapy, a total of three blood culture sets, ideally with the first separated from the last by at least 1 hour, should be sent from different venipuncture sites over 24 hours.

- If the cultures remain negative after 48 to 72 hours, two or three additional blood cultures, including a lysis-centrifugation culture, should be sent.
- Empirical antimicrobial therapy should be withheld in hemodynamically stable patients with subacute endocarditis, especially those who have received antibiotics within the preceding 2 weeks. This will allow additional blood cultures to be sent without the confounding effect of antibiotic therapy.
- Antibiotics should be started immediately in acute endocarditis and in those with hemodynamic instability after the initial three sets of blood cultures are obtained.

ECG

- It should be done for all to serve as a baseline and to detect any complications like conduction abnormalities, MI, and pericarditis.

Echocardiography

- Echocardiography can identify the presence and size of vegetations, detect intracardiac complications, and assess cardiac function. Echocardiography should be done for all patients with a clinical diagnosis of endocarditis.
- Transthoracic echocardiography (TTE) is noninvasive but cannot detect vegetations <2 mm in diameter. It is also not very useful in obese and emphysema patients. TTE is not adequate for evaluating prosthetic valves or detecting intracardiac complications.
- Transesophageal echocardiography (TEE) is more sensitive than TTE. It can detect small vegetations; detect prosthetic endocarditis and intracardiac complications like myocardial abscess, valve perforation, or intracardiac fistulae.

Other Tests

- *Serologic tests* are useful for organisms, which are difficult to culture such as brucella, Bartonella, Legionella, and *Coxiella burnetii.*
- *Culture, microscopic examination and PCR tests* can also be done on vegetations to identify the causative organism.
- Complete blood count may show anemia and increased WBC counts.
- *Urine examination* may show microscopic hematuria (due to renal emboli or focal glomerulonephritis) or macroscopic hematuria (due to renal infarction).
- *Urea and creatinine* may be elevated due to glomerulonephritis.
- *Chest X-ray* may show emboli, cardiac enlargement, and other abnormalities.
- *ESR, CRP, circulating immune complex titer, and rheumatoid factor* concentration are commonly increased in endocarditis.
- *Cardiac catheterization* is useful to assess coronary artery patency in older individuals who are to undergo surgery for endocarditis because CABG also can be done in the same sitting.

Treatment

Antimicrobial Therapy

- Effective antimicrobial therapy for endocarditis requires identification of the specific pathogen and assessment of its susceptibility to various antimicrobial agents. Therefore, every effort must be made to isolate the pathogen before initiating antimicrobial therapy, if clinically feasible.

Table 3.21 Antibiotic regimens for infective endocarditis

Organism	Antibiotic	Dose and duration
Viridans streptococci and *Strep. bovis*	Benzyl penicillin and gentamicin	1.2 g 4-hourly and 1 mg/kg 8–12-hourly for 4–6 weeks
Enterococci		
Ampicillin-sensitive	Ampicillin and gentamicin	2 g 4-hourly and 1 mg/kg 8–12-hourly for 4–6 weeks
Ampicillin-resistant	Vancomycin and gentamicin	1 g 12-hourly and 1 mg/kg 8–12-hourly for 4–6 weeks
Staphylococci		
Penicillin-sensitive	Benzyl penicillin IV	1.2 g 4-hourly for 4–6 weeks
Penicillin-resistant but methicillin-sensitive	Flucloxacillin IV	2 g 4-hourly (<85 kg 6-hourly) for 4–6 weeks
Both penicillin and methicillin-resistant	Vancomycin IV and gentamicin IV	1 g 12-hourly and 1 mg/kg 8-hourly for 4–6 weeks

- In patients with acute endocarditis and hemodynamic instability, empirical antibiotic therapy should be started as soon as possible after obtaining blood cultures. Empirical therapy should be targeted at the most likely pathogens in that particular clinical setting.
- It is difficult to eradicate bacteria from the avascular vegetation in infective endocarditis because this site is relatively inaccessible to host defenses. Bactericidal drugs should be used to kill all the bacteria in the vegetations. Antibiotics should be given parenterally in high doses. Prosthetic valve endocarditis requires longer duration of therapy.
- In most patients, effective antibiotic therapy results in subjective improvement and resolution of fever within 5 to 7 days. Blood cultures should be done daily, and whenever there is fever and 4 to 6 weeks after therapy to document cure. When fever persists for 7 days in spite of appropriate antibiotic therapy, patients should be evaluated for complications of infective endocarditis such as paravalvular abscess, and extracardiac abscesses (spleen, kidney).
- Vegetations become smaller with effective therapy, but some may remain unchanged. Patients who become afebrile during therapy without any complications can complete remaining therapy as outpatients.
- Serologic abnormalities (e.g. erythrocyte sedimentation rate, rheumatoid factor) resolve slowly and do not reflect response to treatment.

Surgery

Indications for Surgery

- Patients with direct extension of infection to myocardial structures.
- Prosthetic valve dysfunction.
- Congestive heart failure from valvular damage.
- Badly damaged valve (requires replacement).
- Endocarditis caused by fungi or by gram-negative or resistant organisms.
- Patients with recurrent (two or more) embolic events.
- Large vegetations (>10 mm) on echocardiography.
- Emergency surgery is required for new onset acute aortic regurgitation and mitral valve and sinus of Valsalva abscess ruptured into right heart.

Relative contraindications to valve replacement are

- Recent massive stroke (because of the risk of bleeding in the perioperative period when anticoagulation is required).
- Multiple prior valve replacements (because of the difficulty of sewing a new valve into tissue already weakened from previous surgeries)
- Ongoing intravenous drug abuse.

Complications of infective endocarditis

- ***Heart failure***: This is the most frequent major complication of IE.
- ***Embolization***: The brain and the spleen are the most common sites of embolization in left-sided IE, whereas septic pulmonary emboli are common in right-sided IE.
- ***Mycotic aneurysms***: These occur due to septic embolization to the arterial vasa vasorum, with subsequent spread of infection and weakening of the vessel wall. They occur most frequently in the intracranial arteries and have a particular predilection for the middle cerebral artery and its branches. Mycotic aneurysms are extremely dangerous, because they can rupture and produce sudden intracranial hemorrhage.
- ***Periannular extension of infection***: Leads to abscess formation, perforation, fistula development, and hemodynamic deterioration. Persistent fever and bacteremia despite antibiotic therapy, heart failure, or new conduction block should raise suspicion for this complication.
- ***Renal dysfunction*** is a common complication of IE and is often multifactorial due to immune complex deposition, drug-induced nephrotoxicity, and hemodynamic perturbations.

Prognosis

- Poor prognosis is seen in older age, severe comorbid conditions, delayed diagnosis, involvement of prosthetic valves or the aortic valve, an invasive (*S. aureus*) or antibiotic-resistant (*P. aeruginosa*, yeast) pathogen, intracardiac complications, and major neurologic complications.

Q. Infective endocarditis prophylaxis.

- Since bacteremia is the first step in the causation of infective endocarditis, prevention of bacteremia can prevent the occurrence of infective endocarditis. Bacteremia is prevented by the administration of antibiotics prior to any procedure known to produce bacteremia. However, not all cardiac lesions are prone for infection. Hence, prophylaxis is recommended only in specific lesions.
- The revised guidelines have narrowed the procedures for which antibiotic prophylaxis is recommended. Antibiotic prophylaxis is no longer recommended for GI/genitourinary tract procedures (including diagnostic esophagogastroduodenoscopy or colonoscopy).

High-risk cardiac conditions requiring antibiotic prophylaxis (latest guidelines)

- Prosthetic cardiac valve
- Previous infective endocarditis

Congenital heart disease (CHD)
- Unrepaired cyanotic CHD, including palliative shunts and conduits.
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure.
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization).

- Cardiac transplantation recipients with cardiac valvular disease.

Procedures which require infective endocarditis prophylaxis

- ***Dental***: All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. The following procedures and events do not need antibiotic prophylaxis: Routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.
- ***Respiratory tract***: Invasive procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa, such as tonsillectomy or adenoidectomy. Routine prophylaxis for bronchoscopy is not recommended unless the procedure involves incision of the respiratory tract mucosa.
- ***Infected skin or musculoskeletal***: Surgical procedures that involve infected skin, skin structure, or musculoskeletal tissue.

Table 3.22 Antibiotic regimens for IE prophylaxis

Situation	Agent and dose (single dose 30–60 min before procedure)
Able to take oral medication	Amoxicillin 2 g
Unable to take oral medication	Ampicillin 2 g IM or IV *or* Cefazolin *or* Ceftriaxone 1 g IM or IV
Allergic to penicillins or ampicillin and able to take orally	Cephalexin 2 g or other first- or second-generation cephalosporin *or* Clindamycin 600 mg *or* Azithromycin *or* Clarithromycin 500 mg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin *or* Ceftriaxone 1 g IM *or* IV *or* Clindamycin 600 mg IM *or* IV

Q. Janeway leisons.

Q. Osler's nodes.

Q. Roth's spots.

- ***Janeway lesions*** are due to septic emboli to skin seen in infective endocarditis. They are macular, blanching, nonpainful, erythematous lesions seen on the palms and soles.
- ***Osler's nodes*** are painful, violaceous nodules found in the pulp of fingers and toes and are seen more often in subacute than acute cases of IE. They are due to immune complex deposition in the skin.
- ***Roth's spots*** are exudative, edematous, oval hemorrhagic lesions with a white center, seen on retina in infective endocarditis. They are due to emboli occluding small retinal vessels.

Q. Libman-Sacks endocarditis (verrucous, marantic, or nonbacterial thrombotic endocarditis).

- Libman-Sacks endocarditis (otherwise known as verrucous, marantic, or nonbacterial thrombotic endocarditis) was first described by Libman and Sacks. It is characterized by atypical, sterile, verrucous vegetations.
- Libman-Sacks endocarditis is the most characteristic cardiac manifestation of the autoimmune disease—systemic lupus erythematosus. It also occurs in association with antiphospholipid antibody (APLA) syndrome, malignancy and hypercoagulable states.
- The verrucae are common on the aortic and mitral valves and usually affect the edge of the valves. They consist of accumulations of immune complexes, mononuclear cells, hematoxylin bodies, and fibrin and platelet thrombi.
- Healing leads to fibrosis, scarring, and calcification. If the scarring is extensive, it may lead to valve deformity, stenotic or regurgitant lesions.
- Verrucous endocarditis is usually asymptomatic. However, the verrucae can fragment and produce systemic emboli, and infective endocarditis can develop on already damaged valves.
- Treatment involves the management of underlying condition. Anticoagulation may be required if there is atrial fibrillation. Valve surgery may be required for hemodynamically significant valvular dysfunction.

Q. Discuss the etiology, classification, and general clinical features of congenital heart diseases.

- Congenital heart disease affects about 1% of live births.

- Males are affected more commonly except atrial septal defect (ASD) and persistent ductus arteriosus (PDA) which are more common in females.
- Because of improved medical and surgical management, more children with congenital heart disease are surviving into adolescence and adulthood.

Etiology

- Congenital heart diseases are due to abnormal development of a normal structure, or failure of a normal structure to develop fully. Such maldevelopments are due to multifactorial genetic and environmental causes. The recognized risk factors include:
  - *Maternal infections*, e.g. rubella infection (persistent ductus arteriosus, and pulmonary valvular and arterial stenosis).
  - *Drugs*: Alcohol abuse (septal defects), phenytoin (associated with pulmonary stenosis) and radiation.
  - *Genetic abnormalities*, e.g. familial form of atrial septal defect and congenital heart block.
  - *Chromosomal abnormalities*, e.g. septal defects and tetralogy of Fallot are associated with Down's syndrome (trisomy 21) or coarctation of the aorta in Turner's syndrome (45, XO).

Classification

Table 3.23 Classification of congenital heart disease

Cyanotic congenital heart diseases	Acyanotic congenital heart diseases
• Fallot's tetralogy • Transposition of the great vessels • Severe Ebstein's anomaly • Severe pulmonary stenosis • Tricuspid atresia	• Atrial septal defect (ASD) • Ventricular septal defect (VSD) • Patent ductus arteriosus (PDA) • Partial anomalous venous drainage • Coarctation of the aorta • Aortic stenosis • Congenital pulmonary valve regurgitation • Pulmonary stenosis

General Clinical Features of Congenital Heart Diseases

- Congenital heart disease (CHD) should be recognized as early as possible, since early treatment is associated with better outcome. Some general clinical features of congenital heart diseases are as follows:
- In as many as 80% of infants with critical disease, congestive heart failure is the presenting symptom. Difficulty in feeding is common and is often associated with tachypnea, sweating and subcostal retraction. Suspicion of CHD should be raised if feeding takes more than 30 minutes. A history of feeding difficulty often precedes overt congestive heart failure. On examination, signs of congestive heart failure include an S3 gallop and crepitations in the lungs.
  - *Central cyanosis* occurs in cyanotic congenital heart diseases because of right-to-left shunting of blood or because of mixing of systemic and pulmonary blood flow.
  - *Pulmonary hypertension* can happen in left-to-right shunts. Blood from left side of the heart under high pressure enters right side and then into pulmonary artery. This leads to pulmonary hypertension. Pressure in the pulmonary arterial system can exceed that on left side of the heart which can cause reversal of blood flow from right side to left side. This reversal of blood flow is reffered to as *Eisenmenger's syndrome.*
  - *Clubbing of the fingers* occurs due to prolonged cyanosis in cyanotic congenital heart diseases.
  - *Paradoxical embolism* of thrombus can occur from systemic veins to systemic arterial system when there is a communication between the right and left heart. This can lead to an increased risk of cerebrovascular accidents and abscesses.
  - *Polycythaemia* can develop secondary to chronic hypoxemia, which lead to hyperviscosity and increased risk of thromboembolism and strokes.
  - *Growth retardation* is common in children with cyanotic heart disease.
  - *Syncope* is common when severe right or left ventricular outflow tract obstruction is present. Exertional syncope, associated with deepening central cyanosis, may occur in Fallot's tetralogy. Exercise increases pulmonary vascular resistance and decreases systemic vascular resistance. Thus, the right-to-left shunt increases and cerebral oxygenation falls.
  - *Squatting* posture is often adopted by children with Fallot's tetralogy. It results in decreased venous return and an increase in the peripheral vascular resistance. This leads to decreased pressure in the right side of heart and increased pressure in left side of the heart which results in reduced right-to-left shunt and improved cerebral oxygenation.
  - *Endocarditis* can occur at the sites of shunts and damaged valves.
  - *Atrial and ventricular arrhythmias, right heart failure* due to pulmonary HTN, *end-stage heart failure and sudden cardiac death* can occur. This may be the first time that the presence of cong heart disease is noted.

Genetic Counseling

- A woman with congential heart disease needs close follow-up during pregnancy. Pregnancy is usually safe except if pulmonary hypertension is present when the prognosis for both mother and fetus is poor.
- Fetal ultrasound screening during pregnancy is necessary to rule out any heart malformations since patients with congenital heart disease are more likely to have a baby with congenital heart disease.

Q. Ventricular septal defect (VSD).

- VSD is the most common congenital heart disease (1 in 500 live births). It may occur as an isolated anomaly or in association with other anomalies.
- Membranous VSD is the most common type. VSD can close spontaneously or lead to congestive cardiac failure and death in infancy.
- Maladie-de-Roger is a small VSD in muscular portion presenting in older children. It produces a loud pansystolic murmur without any hemodynamic consequences. This defect usually closes spontaneously.

Pathophysiology

- As left ventricular pressure is higher than right ventricular pressure, blood moves from left to right leading to increased blood flow through pulmonary vasculature. This increased flow leads to pulmonary HTN and increased right ventricular pressure so much that right ventricular pressure may be equal to or more than left ventricular pressure (Eisenmenger's complex). As a result, the shunt is reduced or reversed (becoming right-to-left) and central cyanosis may develop.

Clinical Features

- *Small VSDs* are asymptomatic and 90% of them close spontaneously by 10 years of age.
- *Moderate and large VSD* leads to pulmonary HTN (Eisenmenger's syndrome), which causes exertional dyspnea, chest pain, syncope, and hemoptysis.
- When there is reversal of shunt (right-to-left shunt), central cyanosis, clubbing, and polycythemia develop.
- CVS examination reveals cardiac enlargement and a prominent apex beat. There is often a palpable systolic thrill at the lower left sternal edge. A loud pansystolic murmur is heard in the same area.

Complications

- Congestive cardiac failure.
- Pulmonary hypertension.
- Eisenmenger's syndrome.
- Infective endocarditis.
- Right ventricular outflow tract obstruction.

Investigations

- *Chest X-ray* may show features of increased pulmonary flow and pulmonary HTN such as prominent pulmonary artery, 'pruned' pulmonary arteries, and right ventricular hypertrophy.
- *ECG* shows features of both left and right ventricular hypertrophy.
- 2D echocardiography and color Doppler can confirm the presence, size and location of the VSD, and abnormal blood flow.

Treatment

- Surgery is not recommended for patients with small shunts and normal pulmonary arterial pressures.
- Surgical correction is indicated for moderate to large VSD before the development of severe pulmonary HTN. If severe pulmonary HTN has developed already, it will not reverse or may progress even after surgery.

Q. Atrial septal defect (ASD).

- ASD is a defect in interatrial septum. It is common in females.

Types of ASD

- There are three main types of ASD, *sinus venosus type*, *ostium secundum* and *ostium primum.*
- Sinus venosus type occurs high in the atrial septum near the entry of the superior vena cava.
- Ostium secundum defect involves the fossa ovalis in the atrial mid-septum and is the most common ASD. Patent foramen ovale (PFO) is a normal variant and not a true septal defect. PFO is usually asymptomatic but can be associated with paradoxical emboli and an increased incidence of embolic stroke.
- Ostium primum type septal defect occurs immediately adjacent to the atrioventricular valves. It is common in patients with Down's syndrome.
- Lutembachers syndrome is a rare combination of ASD with rheumatic mitral stenosis.

Pathophysiology

- ASD allows shunting of blood from high pressure left atrium to low pressure right atrium. Hence, there is increase in right ventricular inflow, right ventricular output, and pulmonary blood flow.
- Increased pulmonary blood flow gives rise to increased pulmonary vascular resistance and pulmonary HTN. This usually happens above the age of 30 years.

- Severe pulmonary HTN may lead to increased right atrial pressure, which can be more than left atrium and lead to right to left shunting with central cyanosis. Ultimately, heart failure may develop due to overloading of both ventricles.
- Because of increased blood flow into right side, right atrium and right ventricles dilate and there may be atrial arrhythmias, especially atrial fibrillation.

Clinical Features

Symptoms

- Children with ASD are asymptomatic, but as they reach 3rd decade, they may develop pulmonary HTN as explained above.
- Dyspnea and weakness occur due to pulmonary HTN.
- Recurrent respiratory infections are common due to increased blood flow through pulmonary vasulature and congestion.
- Palpitations may be experienced due to atrial arrhythmias (atrial fibrillation).

Signs

- Precordium is hyperdynamic.
- Signs of pulmonary HTN such as right ventricular heave, prominent pulmonary artery pulsations may be noted.
- On auscultation, the second heart sound is widely split and fixed in relation to respiration. A mid-diastolic rumbling murmur is heard at the fourth intercostal space and along the left sternal border due to increased flow across the tricuspid valve. An ejection systolic murmur may be heard over pulmonary area due to increased blood flow across pulmonary valve.
- Right heart failure may develop and lead to raised JVP and peripheral edema.
- Development of Eisenmenger's syndrome leads to central cyanosis and digital clubbing.

Complications

- Congestive cardiac failure.
- Pulmonary hypertension.
- Eisenmengers syndrome.
- Infective endocarditis.
- Atrial fibrillation.
- Paradoxical embolism.

Investigations

- ***Chest X-ray*** shows prominent pulmonary artery and pulmonary vascular congestion. It may also show right atrial and right ventricular enlargement.
- ***ECG*** may show right bundle branch block and right axis deviation due to right ventricular hypertrophy and dilatation.
- ***Echocardiogram*** may show right ventricular hypertrophy, dilated pulmonary artery, and abnormal motion of the interventricular septum. It may also show ASD. Abnormal shunt and blood flow can be assessed by color Doppler.
- ***Cardiac catheterization*** can confirm the presence of ASD but usually echo is enough for confirmation. However, it is especially useful when associated coronary artery disease is present as both coronary arteries and ASD can be assessed in the same sitting. Cardiac catheterization shows increased oxygen content of right atrial blood due to blood flow from left atrium.

Treatment

- Surgical closure should be done between 3 and 6 years of age or as soon as possible in significant ASD (i.e. pulmonary flow more than 50% increased compared with systemic flow).
- Closure should not be carried out in patients with small defects and trivial left-to-right shunts or in those with severe pulmonary hypertension.
- Angiographic closure is now possible by using a transcatheter device.
- Uncorrected ASDs do not usually require antibiotic prophylaxis for endocarditis unless there is another accompanying valvular lesion.

Q. Patent ductus arteriosus (PDA).

- The ductus arteriosus is a vessel, which connects the pulmonary artery to the descending aorta distal to the subclavian artery.
- In fetal life, the ductus arteriosus is normally open and diverts blood away from the unexpanded and hence high resistance pulmonary circulation into the systemic circulation, where the blood is re-oxygenated as it passes through the placenta.
- The duct normally closes at birth, due to high oxygen in the lungs and the reduced pulmonary vascular resistance. After closure a fibrous band is left behind (ligamentum arteriosum).
- If the duct is defective (e.g. less elastic tissue) it will not close. Prenatal hypoxemia and high-altitude environments may impair closure of ductus.
- PDA is more common in females and is sometimes associated with maternal rubella. Premature babies can have PDA which is normal and will close later.

Pathophysiology

- Since pressure in the aorta is more than pulmonary artery, blood flows from aorta to pulmonary artery throughout the cardiac cycle. This leads to increased flow through the pulmonary vasculature leading to pulmonary HTN.
- Left heart also gets overloaded due to increased pulmonary venous return which may result in left heart failure.
- If pulmonary HTN is very severe, it may lead to reversal of flow from pulmonary artery to aorta (Eisenmenger's physiology).
- One-third of patients with PDA die of heart failure, pulmonary hypertension or endocarditis by the age of 40; two-thirds by the age of 60.

Clinical Features

- Patients may remain asympomatic until later in life when heart failure or infective endocarditis develops.
- High volume peripheral pulses ('bounding') may be noted due to increased venous return to left heart and hence increased stroke volume.
- Auscultation reveals a characteristic continuous 'machinery' murmur heard at the first or second left intercostal space.
- Signs of pulmonary HTN such as loud P2, parasternal heave and prominent epigastric pulsations may be present.
- In patients with reversal of shunt (Eisenmenger's physiology), venous blood from pulmonary artery enters descending aorta and leads to differential cyanosis, i.e. a cyanois in the lower limbs and sparing of upper limbs especially the right arm.

Complications

- Congestive cardiac failure
- Pulmonary hypertension
- Eisenmenger's syndrome
- Infective endocarditis
- Paradoxical embolism
- Rupture of the ductus

Investigations

- *Chest X-ray* may show promonent aorta and pulmonary arterial system. It may also show dilated left atrium and ventricle.
- *ECG* shows left ventricular hypertrophy.
- *Echocardiogram* shows dilated left atrium and left ventricle. Color Doppler can visualize PDA and direction of blood flow.

Treatment

- Premature infants with PDA are treated medically with indomethacin. Indomethăcin closes PDA by inhibiting prostaglandin production which maintains patency.
- In other cases, PDA can be closed surgically or via transcatheter methods. Surgery should be done as soon as possible and before the age of 5 years. Closure should not be done if Eisenmenger's physiology has developed.

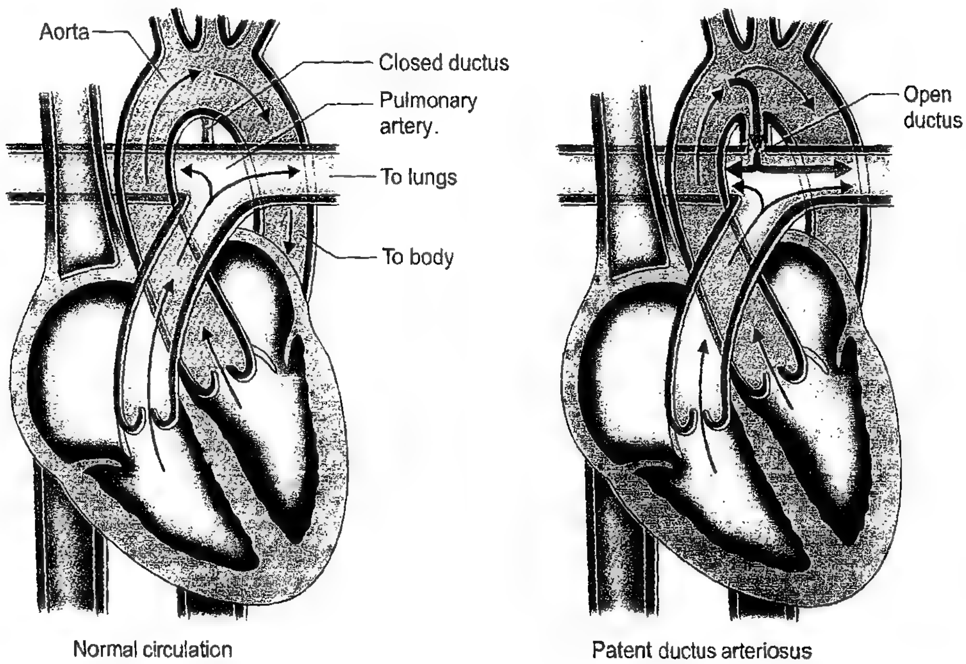

Fig. 3.5: Patent ductus arteriosus

Q. Coarctation of the aorta.

- Coarctation of the aorta refers to narrowing of the aorta. It usually occurs at or just distal to the insertion of ligamentum arteriosum, i.e. distal to the left subclavian artery. Rarely it can occur proximal to the left subclavian artery.
- It is two times more common in men than in women. It is also associated with Turner's syndrome. Other coexisting anomalies are bicuspid aortic valve (most common), VSD and PDA. "Pseudocoarctation" refers to buckling or kinking of the aortic arch without the presence of a significant gradient.

Pathophysiology

- Coarctation causes obstruction of blood flow in the descending thoracic aorta. This leads to the formation of collateral circulation from the internal mammary, scapular, and superior intercostal arteries to the intercostals of the descending aorta. Decreased renal perfusion activates rennin angiotensin system which leads to the development of hypertension. Lower part of the body may receive less blood supply which leads to growth impairment.

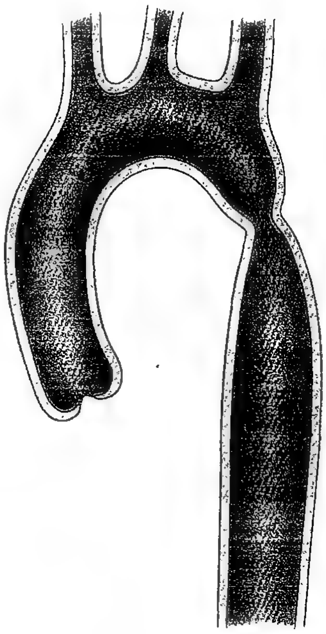

Fig. 3.6: Coarctation of the aorta

Clinical Features

- Coarctation of the aorta is often asymptomatic for many years. Patients may present with headache, epistaxis (due to hypertension) and claudication, leg fatigue, and cold legs (due to poor blood flow to lower limbs). Older patients may present with angina and symptoms of heart failure.
- Physical examination shows prominent pulsations in the neck. Suzman's sign is dilated, tortuous, pulsatile arteries seen around the scapulae and intercostals spaces in the back. It is better seen when the patient bends forward with hands lying down. Lower half of the body is less developed than the upper half. The hips are narrow and the legs are short, in contrast to broad shoulders and long arms. Blood pressure should be measured in both arms and any one leg. There is high pressure in the arms and low pressure in the legs. There are weak pulses in lower limbs and radiofemoral delay. Signs of LVH may be noted.

Investigations

- Chest X-ray may show dilated aorta indented at the site of the coarctation, which gives it the appearance of 'figure 3'. Dilated intercostal arteries due to collateral flow may erode the undersurfaces of the ribs and cause rib notching (Docks sign).
- ECG shows left ventricular hypertrophy.
- Echocardiography shows the gradient in the descending aorta, LVH and other associated anomalies.
- MRI is the best modality for visualizing the anatomy of the descending aorta.
- Cardiac catheterization can measure pressures and assess collaterals when surgery is planned.
- Aortography can also show the exact site of coarctation.

Complications

- Left ventricular failure
- Hypertension
- Cerebral aneurysm and hemorrhage
- Infective endocarditis at the site of coarctation
- Aortic dissection and rupture of aorta.

Treatment

- Intervention is indicated if the pressure gradient across the coarctation is more than 30 mm Hg.
- Treatment involves surgical excision of the coarctation and end-to-end anastomosis of the aorta.
- Balloon dilatation is used in some centers either for initial treatment or for recurrence of coarctation. The incidence of incomplete relief and restenosis is decreased by endovascular stent placement.

Q. Tetralogy of Fallot (TOF).

- Fallot's tetralogy is the most common cyanotic congenital heart disease. It is characterized by 4 features; pulmonary stenosis, VSD, overriding aorta, and right ventricular hypertrophy. Pulmonary stenosis can be subvalvular (commonest), valvular or supravalvular.

- Presence of ASD along with TOF is called pentology of Fallot.

Pathophysiology

- Since the right ventricular pressure is more than left ventricle due to pulmonary stenosis, blood is shunted from right to left through the ventricular septal defect, which leads to central cyanosis. Squatting episodes increase systemic arterial rsistance and hence reduce the shunt from right to left ventricle.

Clinical Features

- Children are usually asymptomatic at birth
- Children with Fallot's tetrology may present with dyspnea and fatigue.
- Growth is usually retarded
- Exercise leads to drop in systemic vascular resistance and increases the shunting of blood from right to left ventricle leading to increased cyanosis and syncope (cyanotic or Fallot's spells). Cyanotic spells occur during crying, feeding, exercise and fever. Sudden death can occur during such spells.
- Squatting is common because it increases peripheral vascular resistance and decreases shunt.
- Polycythemia and clubbing occur due to chronic hypoxemia which may result in thrombotic strokes.
- A parasternal heave is common due to RVH.
- P2 is faint or inaudible. An ejection sound from aortic dilation and a diastolic murmur from consequent aortic regurgitation can be heard. VSD murmur is not heard because it is large.

Investigations

- ***Chest X-ray*** shows "boot-shaped heart" heart. This shape results from small concave pulmonary artery and hypertrophied right ventricle coupled with small to normal-sized left ventricle with upturned apex. Pulmonary vascularity is reduced.
- ***ECG*** shows right ventricular hypertrophy and right-axis deviation. Right bundle branch block may also be present.
- ***Echocardiogram*** can readily identify overriding aorta and VSD. The degree of pulmonary stenosis and VSD are best assessed by Doppler.
- ***Cardiac catheterization*** is done for patients in whom operative treatment is contemplated or in whom the integrity of the coronary circulation needs to be verified.

Complications

- Intravascular thrombosis and thrombotic stroke can occur.
- Brain abscess can occur because organisms entering right ventricle by venous return can enter systemic circulation through VSD and reach brain.
- Infective endocarditis.
- Higher incidence of pulmonary tuberculosis.

Treatment

- Complete surgical repair consists of patch closure of the VSD and relief of pulmonary stenosis.
- Occasionally a palliative procedure—an anastomosis between subclavian artery and pulmonary artery (Blalock-Taussig shunt)—is performed on very young or premature infants.
- Antibiotic prophylaxis for endocarditis is needed.

Q. What is Eisenmenger's syndrome? Discuss the clinical features, investigations and management of Eisenmenger's syndrome.

Definition

- Eisenmenger's syndrome is defined as pulmonary vascular obstructive disease that develops as a consequence of a large pre-existing left-to-right shunt such that pulmonary artery pressures approach systemic levels and the direction of the flow becomes bidirectional or right to left. Right to left shunting of blood leads to central cyanosis.
- Congenital heart defects which can cause Eisenmenger's syndrome are ASD, VSD, PDA, truncus arteriosus, aorto-pulmonary window, and univentricular heart.

Clinical Features

- Patients may present with dyspnea on exertion, syncope, chest pain, congestive heart failure, hemoptysis and symptoms related to polycythemia and hyperviscosity.
- On examination, central cyanosis and clubbing are present. Parasternal heave and epigastric pulsations are felt due to right ventricular hypertrophy. Pulmonary artery pulsation is commonly felt. P2 is loud and may be palpable. A tricuspid regurgitation murmur is common, due to right ventricular dilatation. In addition to these, features of underlying congenital heart defect may be noted.

Investigations

- ***ECG*** shows evidence of right atrial enlargement, right ventricular hypertrophy, and right axis deviation.
- ***Chest X-ray*** shows dilated pulmonary artery, cardio-megaly, and pulmonary oligemia.
- ***Echocardiography*** confirms the right-sided pressure overload and pulmonary artery enlargement, as well as the intracardiac defect with right to left shunting.

- *Cardiac catheterization* can directly measure pulmonary artery pressure and also assess the reversibility of the elevated pulmonary vascular resistance after giving vasodilators which is useful to decide whether a patient benefits from surgery.

Treatment

- Eisenmenger's syndrome is the only type of pulmonary artery hypertension, where its development is preventable by early closure of underlying defect. On the other hand, once it develops, closure of the underlying defect is contraindicated.
- The main interventions are directed toward preventing complications such as influenza vaccine to prevent respiratory infections, iron replacement for iron deficiency; antiarrhythmics for atrial arrhythmias, digoxin and diuretics for right-sided heart failure.
- When patients are severely incapacitated from severe hypoxemia or congestive heart failure, lung transplantation (plus repair of the cardiac defect) or heart-lung transplantation may be considered.

Q. Transposition of the great arteries (TGA).

- Complete TGA is the second most common congenital heart defect.
- Here the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. This defect causes deoxygenated blood to enter systemic circulation, and oxygenated blood to enter pulmonary circulation. Since both systemic and pulmonary circulations are not connected with each other, this condition is incompatible with life unless a VSD, PDA, or ASD is present or an ASD is created.

Clinical Features

- Severe cyanosis is the presenting sign, making its clinical appearance within the first few hours after birth. Neonates who have a communication between right and left heart due to a persistent PDA, ASD or VSD, patent foramen ovale, etc. may survive for a few weeks and present later.
- Examination shows intense cyanosis and tachypnea. The right ventricular lift is forceful, and the first sound is usually loud at the lower left sternal border. Signs of heart failure may be present.

Investigations

- ***Chest X-ray***: Cardiomegaly, pulmonary plethora may be seen.
- ***ECG*** may show abnormal right axis deviation and marked right ventricular hypertrophy.
- ***Echocardiogram***: Confirms the presence of TGA.
- ***Cardiac catheterization*** may be necessary to evaluate the coronary artery pattern and to perform a balloon atrial septostomy to allow mixing of right and left side blood.

Treatment

- ***The atrial switch operation***: The senning or mustard procedure, are the corrective procedures, which redirect oxygenated blood from the left atrium to the right ventricle so that it may be ejected into the aorta while deoxygenated blood enters the right atrium and heads for the left ventricle and into the pulmonary artery.
- ***Rastelli procedure***: Reroutes blood at the ventricular level by tunneling the left ventricle to the aorta inside the heart through a VSD. A conduit is then inserted outside the heart between the left ventricle and aorta.
- ***Arterial switch operation***: Transects the aorta and pulmonary artery above their respective valves and switches them to become realigned with their appropriate ventricles. This is the most physiological procedure.

Q. Marfan's syndrome.

- Marfan's syndrome is an autosomal dominant inherited disorder of connective tissue. It occurs due to mutation of Marfan's syndrome type 1 (MFS1) gene for fibrillin on chromosome 15q21. It affects approximately 1 in 5000 population.

Clinical Features

- Marfan's syndrome affects the heart (aortic aneurysm and dissection, mitral valve prolapse), eye (dislocated lenses, retinal detachment) and skeleton (tall, thin body build with long arms, legs and fingers; scoliosis and pectus deformity). For clinical diagnosis, two out of three major systems should be affected. Diagnosis can be confirmed by demonstrating a mutation in the Marfan's syndrome type 1 (MFS1) gene for fibrillin on chromosome 15q21.

Investigations

- Chest X-ray may be normal or show signs of aortic aneurysm and widened mediastinum. Scoliosis may also be seen.
- Echocardiography shows mitral valve prolapse, mitral regurgitation, and aortic root dilatation.
- Genetic study to demonstrate Marfan's syndrome type 1 (MFS1) gene.

Management

- Beta blocker therapy slows the rate of dilatation of the aortic root.

- Prolonged exertion should be avoided because of cardiac defects.
- Aortic root diameter of 5 cm or more requires aortic root replacement.

Q. Discuss the etiology (risk factors) of ischemic heart disease (IHD).

- IHD is a life-threatening disease and an expensive disease.
- There are many risk factors for IHD. Some are modifiable and some are not modifiable.
- Atherosclerosis is responsible for almost all cases of IHD. Most risk factors act by promoting atherosclerosis of the coronary arteries.
- An overview of the established and emerging risk factors for cardiovascular disease is given below.

Risk Factors for IHD

- ***Dyslipidemia***: Elevated LDL-cholesterol, low HDL-cholesterol, increased total-to-HDL-cholesterol ratio, hypertriglyceridemia are associated with increased risk of IHD.
- ***Hypertension***: This is a well-established risk factor for IHD. Both systolic and diastolic blood pressures are important. Isolated systolic hypertension is now established as a risk factor for coronary heart disease and stroke.
- ***Diabetes mellitus***: Insulin resistance, hyperinsulinemia, and elevated blood glucose are associated with atherosclerotic cardiovascular disease and IHD.
- ***Obesity***: Obesity is associated with a number of risk factors for atherosclerosis, such as hypertension, insulin resistance and glucose intolerance, hypertriglyceridemia, and reduced HDL-cholesterol.
- ***Metabolic syndrome***: Patients with the constellation of abdominal obesity, hypertension, diabetes, and dyslipidemia are considered to have the metabolic syndrome (syndrome X). Metabolic syndrome is associated with higher risk of coronary artery disease.
- ***Sedentary life style***: This leads to obesity, impaired glucose tolerance and is a risk factor for IHD.
- ***Smoking***: Cigarette smoking is an important and reversible risk factor. The incidence of an MI is increased sixfold in women and threefold in men who smoke at least 20 cigarettes per day compared to subjects who never smoked.
- ***Aging***: As the age advances, atherosclerosis of vessels also increases. Most of the IHD cases occur after 40 years of age. Aging is an independent risk factor for IHD.
- ***Family history***: Family history is a significant independent risk factor for IHD, particularly among younger individuals with a family history of premature disease.
- ***Socioeconomic factors***: Low socioeconomic status is associated with higher risk.
- ***Chronic kidney disease***: Patients with chronic kidney disease have higher risk of IHD.
- ***Diet factors***: A diet rich in calories, saturated fat, and cholesterol is a risk factor for IHD.
- ***Psychosocial factors***: Psychologic stress can lead to premature atherosclerosis and also aggravate traditional risk factors such as smoking, hypertension, and lipid metabolism. People with depression, anger, stress and other factors have higher chances of developing IHD.
- ***C-reactive protein***: A higher level of C-reactive protein (CRP) is associated with higher risk of IHD. CRP is a marker of inflammation which may have a role in promotion of atherosclerosis.
- ***Microalbuminuria***: Microalbuminuria reflects vascular damage and is an important risk factor for cardiovascular disease and early cardiovascular mortality.
- ***Left ventricular hypertrophy***: Left ventricular hypertrophy (LVH), which is associated with hypertension as well as with age and obesity, is a risk factor for IHD.
- ***Homocysteine levels***: An elevated level of homocysteine is associated with increased risk of IHD.
- ***Asymmetrical dimethylarginine (ADMA)*** is an endogenous nitric oxide synthase inhibitor. It is an independent risk factor for endothelial dysfunction and IHD.
- ***Hyperuricemia***: Hyperuricemia is associated with an increased risk of IHD and increased mortality in those with IHD.
- ***Infection***: Certain infections may play a role in the pathogenesis of atherosclerosis by establishing a low-grade persistent inflammatory process of endothelium. Some organisms suspected are *Chlamydia pneumoniae*, cytomegalovirus, and *Helicobacter pylori*.
- ***Collagen vascular disease***: Patients with collagen vascular disease, especially those with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), have a significantly increased incidence of cardiovascular disease.
- ***Air pollution***: Fine particulate air pollution is associated with increased risk of IHD and cardiopulmonary mortality. This may be due to acute arterial vasoconstriction and myocardial ischemia induced by air pollution.

Q. Define angina. Describe the etiology, pathogenesis, clinical features, investigations, and management of angina.

Q. Prinzmetal's angina.

Q. Angina equivalents.

Definition

- Angina pectoris may be defined as a discomfort in the chest and/or adjacent area associated with myocardial ischemia but without myocardial necrosis.
- It is a common presenting symptom among patients with coronary artery disease (CAD).

Types

- ***Stable angina*** is usually reproducible and is consistent over time. It is precipitated by effort, and relieved by rest. Stable angina is caused by fixed stenosis in coronary arteries.
- ***Unstable angina*** is diagnosed when a patient has new-onset angina, worsening angina (angina that is more frequent, more prolonged, or precipitated by less effort than before), or angina occurring at rest.
- ***Prinzmetal's angina*** is due to coronary vasospasm occurring at rest.
- ***Postprandial angina*** develops during or soon after meals because of increased oxygen demand in the splanchnic vascular bed.
- ***Decubitus angina (nocturnal angina)*** is caused by the increase in LV wall stress because of the redistribution of the intravascular blood volume in the recumbent position.

Etiology

- Angina is due to transient decrease in blood supply to myocardium.
- It may be due to fixed coronary stenosis, clot superimposed on a fixed coronary stenosis, or coronary vasospasm. In the absence of collateral circulation, stenoses of more than 75% of the cross-sectional area (corresponding to >50% lumen diameter by angiography) result in stable angina. Chest pain can occur at rest due to severe stenoses or thrombus formation or due to vasospasm as in Prinzmetal's angina.
- Stenosis is most commonly due to atherosclerosis.
- Angina can also occur when myocardial oxygen demand increases inspite of normal coronary arteries. Examples are patients with aortic stenosis or hypertrophic cardiomyopathy who may experience angina due to markedly increased myocardial oxygen demand because of myocardial hypertrophy. Other factors which increase myocardial oxygen demand are anemia, thyrotoxicosis, aortic regurgitation, exercise, and tachycardia.
- Mental stress, emotions, postprandial state, exposure to cold may reduce coronary flow and lead to angina.
- In syndrome X, patients may experience angina due to failure of coronary vasodilatation with exercise.

Pathophysiology

- Myocardial ischemia is caused by an imbalance between myocardial oxygen supply and oxygen demand. Ischemic myocardium releases active substances, such as adenosine and bradykinin, which stimulate pain receptors and impulses are carried by afferent nerves to upper fifth sympathetic ganglia and upper thoracic spinal cord and from there to thalamus and cortex. When the impulses reach thalamus and cortex, patient perceives the discomfort.
- Myocardial oxygen demand depends mainly on heart rate, wall tension during systole (afterload), the inotropic state of the myocardial cell (contractility), and end-diastolic volume (preload). Whenever there is increased oxygen demand, it is met by coronary vasodilation. Coronary blood flow can increase five to sixfold during exercise from resting values of 0.8 ml/g/min. This increase in flow is due to release of substances like adenosine, and nitric oxide (NO) which are potent vasodilators. Coronary perfusion of the left ventricle occurs mainly in diastole due to decreased wall tension and coronary resistance. Wall tension is highest in the subendocardium and lowest in the subepicardium. Hence, subendocardium is more prone to ischemia than epicardium. However, severe ischemia involves full thickness myocardium from endocardium to the epicardium (transmural ischemia).

Clinical Manifestations

History

- Angina means tightening, not pain. Thus, the discomfort of angina is often described as "pressing," "squeezing," "strangling," "constricting," "bursting," and "burning".
- Angina usually builds up within 30 seconds and disappears in 5 to 15 minutes. Pain is usually brought on by exertion. The intensity of pain ranges from mild to severe discomfort. The discomfort is most commonly midsternal and radiates to the neck, left shoulder, and left arm. Rarely it can radiate to the jaw, teeth, right arm, back, and epigastrium.
- The clenching of the fist over the sternum while describing the pain (Levine's sign) is classic.
- Pain may be associated with sweating, palpitations, dizziness and dyspnea.
- There may be history of other comorbid conditions like diabetes and hypertension. Smoking history may be positive.

- *Angina equivalents*: Some patients instead of chest pain or discomfort, experience dyspnea, dizziness, fatigue, or gastrointestinal complaints (epigastric burning, nausea and vomiting). These symptoms are called angina equivalents. When these symptoms occur in response to exercise or other stress, myocardial ischemia should be ruled out.

Physical Examination

- ***General examination*** may show signs of generalized atherosclerosis like tendon xanthoma, xanthelasmas, thickening of Achilles tendon, locomotor brachialis and corneal arcus. Signs of peripheral vascular disease such as absent peripheral pusles may be noted. Heart rate and BP may be elevated. Excessive sweating may be noted.
- ***Systemic examination*** can be completely normal. 3rd and 4th heart sounds; mitral regurgitation murmur (due to ischemic papillary muscle dysfunction) may be heard during ischemia. Paradoxical splitting of S2 (from transient left ventricular dysfunction or left bundle branch block) may be noted. Bilateral basal crepitations may be heard during ischemia due to transient left ventricular dysfunction. Pain is promptly relieved by nitroglycerin. Other systems are usually normal.

Investigations

Resting ECG

- This is usually normal between attacks. During an attack, ST depression and T wave inversions in the leads corresponding to ischemic areas may be seen. Changes of old myocardial infarction such as pathological Q waves, and left bundle branch block may be present.

Exercise ECG (Stress Test)

- Since the resting ECG can be normal in between the attacks, exercise testing can be useful to confirm the diagnosis of angina. Patient is asked to walk on a treadmill and ECG is recorded continuously. Patient may experience chest discomfort during exercise and if ECG shows ST segment depression of >1 mm, it suggests myocardial ischemia. However, a normal test does not exclude coronary artery disease (CAD) (false-negative test) and on the other hand up to 20% of patients with positive exercise tests may not have coronary artery disease (false-positive test).

Cardiac Scintigraphy

- Myocardial perfusion scans at rest and after stress (i.e. exercise or dobutamine), is a sensitive indicator of ischemia and useful in deciding if a stenosis seen at angiography is giving rise to ischemia.

Echocardiography

- Ischemic or infarcted ventricular wall does not move properly. This is called regional wall motion abnormally (RWMA) and reflect ischemia or previous infarction. Stress echocardiography, can be abnormal if resting echo does not show any abnormalities.

Coronary Angiography (CAG)

- When all the above tests do not provide an answer to chest pain, CAG can be useful. It can delineate the exact coronary anatomy and areas of stenosis. It is always done in patients being considered for revascularization (i.e. coronary artery bypass grafting or coronary angioplasty).
- The indications for coronary angiography are as follows:
  - Angina refractory to medical therapy
  - Strongly positive exercise test
  - Unstable angina
  - Angina occurring after myocardial infarction
  - Patients under 50 years with angina or myocardial infarction
  - Where the diagnosis of angina is uncertain
  - Severe left ventricular dysfunction after myocardial infarction
  - Non-Q wave myocardial infarction

Treatment of Angina

General Management

- Patients should be reassured. Comorbid conditions such as anemia, hyperthyroidism, diabetes, hypertension, and hypercholesterolemia should be treated. Smoking should be stopped; regular exercise and low fat diet should be encouraged.

Medical Treatment

Glyceryl trinitrate (GTN)

- Used sublingually, either as a tablet or as a spray, gives prompt relief (peak action 4–8 minutes and lasts 20–30 minutes). If relief is not obtained within 2 or 3 mins after nitroglycerin, a second or third dose may be given at 5-min intervals. It can be given prior to any activity known to induce angina. Transdermal GTN preparations are also available and their action lasts up to 24 hours. All patients with angina require nitrates as regular prophylactic therapy. Oral long acting preparations of nitrates can be used for daily therapy.

Long-acting nitrates (e.g. isosorbide dinitrate and mononitrate)

- These are helpful for long-term prophylactic therapy. They reduce venous return and hence intracardiac diastolic pressures, reduce afterload and dilate coronary

3

arteries. Tolerance with loss of efficacy develops with 12 to 24 hour of continuous exposure to long-acting nitrates. To prevent tolerance, patient should be kept free of nitrates for a minimum of 8 hours each day. Nitrates should be used with caution in patients with low BP. Sildenafil can precipitate hypotension if given to patients taking nitrates.

Antiplatelet agents

- Aspirin inhibits cyclooxygenase activity and inhibits platelet aggregation. It reduces the risk of coronary events in patients with coronary artery disease. All patients with angina should be given aspirin (75–325 mg daily) unless contraindicated. Clopidogrel (300 mg loading and 75 mg daily) is another antiplatelet agent which acts by blocking ADP receptor-mediated platelet aggregation. It is as effective as aspirin and especially useful when aspirin is contraindicated due to allergy, dyspepsia and GI bleed.

Beta blockers

- Beta blockers reduce myocardial oxygen demand by decreasing heart rate (negative chronotropic effect) and the force of ventricular contraction (negative inotropic effect). If there is coexistent hypertension, beta blockers help in controlling that also. All patients with angina should be given beta blockers unless there are contraindications (asthma, heart blocks, COPD). Cardioselective beta blockers like atenolol, metoprolol, carvedilol, and nebivolol are used commonly.

Angiotensin-converting enzyme (ACE) inhibitors

- Clinical trials have shown that ACE inhibitors reduce major adverse events (death, myocardial infarction, and stroke), angina, and the need for revascularization in patients with CAD.

Calcium-channel blockers

- These drugs block calcium flux into the cell. They relax coronary arteries, cause peripheral vasodilatation and reduce the force of left ventricular contraction, thereby reducing myocardial oxygen demand. The non-dihydropyridine calcium antagonists (e.g. diltiazem and verapamil) also reduce the heart rate and are particularly useful antianginal agents. Long-acting dihydropyridines (e.g. amlodipine, felodipine) are also useful as they have a smooth profile of action with no significant effect on the heart rate. Short-acting dihydropyridines (e.g. nifedipine) can cause reflex tachycardia and worsen angina. Case-control studies have shown that long-term nifedipine is associated with adverse outcome and should not be used.

Nicorandil

- This is a potassium-channel activator with a nitrate component. It has both arterial and venous vasodilating properties. It can be used when there are contraindications to other drugs or can be added if angina is not responding to above drugs.

Ranolazine

- This is a cardioselective anti-ischemic agent (piperazine derivative) that partially inhibits fatty acid oxidation. Also inhibits late sodium current into myocardial cells and prolongs QTc interval. Indicated for chronic angina unresponsive to other antianginal treatments. Unlike beta blockers or calcium channel blockers, it does not reduce blood pressure or heart rate.

Coronary angioplasty

- Percutaneous transluminal coronary angioplasty (PTCA) is the technique of dilating coronary stenosis by passing and inflating a balloon inside the stenosis. The balloon is threaded into the site of stenosis by a thin catheter inserted through radial or femoral artery. PTCA improves symptoms of angina, but confers no significant prognostic benefit. Complications of PTCA include mortality (1%), acute myocardial infarction (2%), and the need for urgent coronary artery bypass grafting (CABG) (2%). A stent can be placed at the site of stenosis to prevent restenosis. There are many types of stents available in the market. PTCA plus stent implantation is superior to PTCA alone for reducing cardiovascular events and the need for repeat intervention as restenosis is less after stent placement.

Coronary artery bypass grafting (CABG)

- CABG is indicated when patients remain symptomatic despite optimal medical therapy and whose disease is not suitable for PTCA. CABG dramatically improves angina in about 90% of cases. It is also indicated for patients with severe three-vessel disease (significant proximal stenoses in all three main coronary vessels), and in those with left main stem artery disease. CABG provides improved survival in such situations. Usually the left or right internal mammary artery is used in CABG. Long saphenous vein can also be used but is used less commonly now because of higher risk of atheromatous occlusion.

Transmyocardial laser revascularization (TMR)

- Patients who remain symptomatic despite optimal medical therapy and are not suitable for PTCA or CABG may benefit from transmyocardial laser revascularization (TMR). Here laser is used to make channels (small holes) in the myocardium to allow direct perfusion of the myocardium from blood within the ventricular cavity. However, controlled studies have not shown much benefit.

Q. What are acute coronary syndromes?

- Acute coronary syndromes (ACSs) include:
  - Unstable angina
  - Non-ST-elevation myocardial infarction (NSTEMI)
  - ST-elevation myocardial infarction (STEMI)

Q. Define unstable angina. Describe the etiology, clinical features, investigations, and management of unstable angina.

Q. Non-ST-elevation myocardial infarction (NSTEMI).

Definition

- Unstable angina is defined as angina with at least one of three features: (1) It occurs at rest (or with minimal exertion) usually lasting >10 min, (2) it is severe and of new onset (i.e. within the prior 4 to 6 weeks), and/or (3) it occurs with a crescendo pattern (i.e. previously diagnosed angina that has become distinctly more frequent, longer in duration, or more severe in nature).
- Non-ST-elevation myocardial infarction (NSTEMI) is unstable angina with evidence of myocardial necrosis as evidenced by elevated cardiac biomarkers (CK-MB and troponins). Hence, unstable angina + elevated CKMB/troponin is NSTEMI. In NSTEMI, there will not be any ST elevation on ECG.
- Since the pathogenesis, clinical features and management of both unstable angina and NSTEMI are same, both are described together here.

Etiology

- Unstable angina/NSTEMI is caused by rupture or erosion of the atherosclerotic plaque with formation of partially occlusive thrombus. Progressive atherosclerosis is another cause. Sometimes it is caused by coronary spasm (Prinzmetal's angina) or increase in myocardial oxygen demand superimposed on pre-existing CAD.

Clinical Features

- Patients with unstable angina/NSTEMI present with substernal chest pain. Characteristics of chest pain are same as those of stable angina but more severe. Pain usually radiates to the neck, left shoulder, and left arm.
- Anginal "equivalents" such as dyspnea and epigastric discomfort may also occur.
- Examination may be normal or may show diaphoresis, pale cool skin, sinus tachycardia, third and/or fourth heart sound, bilateral basal crepitations, and sometimes hypotension.

Investigations

- *ECG*: Usually shows ST-segment depression, and/or T-wave inversion in the leads corresponding to ischemic area.
- *Cardiac enzymes*: CK-MB and troponins may be elevated.
- Other investigations are same as stable angina.

Treatment

- Patients with unstable angina/NSTEMI should be admitted to ICU and placed on bedrest. High flow oxygen should be started for all patients. Continuous ECG monitoring should be done to detect ST-segment deviation and any arrhythmias. Medical management involves administration of anti-ischemic and anti-thrombotic treatment.

Antiplatelet agents (aspirin, clopidogrel and ticlopidine, glycoprotein IIB/IIIA inhibitors)

- Platelets play an important role in the formation of thrombus in coronary arteries. When there is rupture of the atheromatous plaque, platelets get exposed to collagen tissue factor, ADP (adenosine diphosphate), thromboxane A2 (TXA2), and thrombin which results platelet activation. Platelet activation leads to the expression of glycoprotein (GP) IIb/IIIa receptors on the platelet surface which leads to platelet aggregation. *Aspirin* prevents platelet aggregation by blocking thromboxane A2 synthesis. All patients with ACS should receive 325 mg loading dose aspirin and then 75–150 mg daily unless contraindicated.
- *Clopidogrel and ticlopidine* are thienopyridines that inhibit ADP-dependent activation of the glycoprotein (GP) IIb/IIIa receptors. A loading dose of 300 mg clopidogrel followed by 75 mg daily along with aspirin is more effective than either drug alone.
- *Abciximab* (a monoclonal antibody), *Eptifibatide, and Tirofiban* are recently developed GP IIb/IIIa receptor antagonists. These are powerful inhibitors of platelet aggregation and can be given intravenously.

Antithrombotic therapy

- Unfractionated heparin should be started at a dose of 5000 U IV bolus, followed by infusion of 1000 U/hour titrated to aPTT 1.5–2.5 times control. Alternatively low molecular weight heparins such as dalteparin or enoxaparin can be used subcutaneously. APTT need not be monitored for low molecular weight heparins.

Other drugs and further treatment for unstable angina is same as stable angina.

Q. Describe the etiopathogenesis, clinical features, diagnosis and management of acute myocardial infarction (STEMI).

- Myocardial infarction (MI) (i.e. heart attack) is the irreversible necrosis of heart muscle secondary to prolonged ischemia. This usually results from an imbalance in oxygen supply and demand, which is most often caused by plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium.
- Myocardial injury is reflected by elevated cardiac enzymes troponin I and T, CK-MB. Two patterns of MI can be recognized based on ECG findings.
- *Non-ST segment elevation MI (NSTEMI)*: This is unstable angina accompanied by elevated markers of myocardial injury, such as troponins and CK-MB, but no ST segment elevation in ECG.
- *ST segment elevation MI (STEMI):* When myocardial injury is accompanied by both enzyme and ST segment elevation it is reffered to as *ST segment elevation MI (STEMI)*.
- It is important to differentiate between non-ST segment elevation MI and ST segment elevation MI because early recanalization therapy improves the outcome in ST elevation MI but not in non-ST segment elevation MI. NSTEMI has been described along with unstable angina. The following description is about STEMI.

Etiology

- Atherosclerosis is the disease responsible for most acute coronary syndrome (ACS) cases including myocardial infarction. Approximately 90% of myocardial infarctions result from an acute thrombus that obstructs an atherosclerotic coronary artery.
- Non-atherosclerotic causes of myocardial infarction include: Coronary occlusion secondary to vasculitis; ventricular hypertrophy (e.g. idiopathic hypertrophic subaortic stenosis, underlying valve disease); coronary artery emboli, secondary to cholesterol, air, or the products of sepsis; congenital coronary anomalies; coronary trauma; coronary vasospasm; drug use (e.g. cocaine, ephedrine), increased oxygen requirement (such as heavy exertion, fever, or hyperthyroidism); decreased oxygen delivery (severe anemia, carbon monoxide posoning); aortic dissection, with retrograde involvement of the coronary arteries.

Pathogenesis

- Rupture or erosion of an atherosclerotic plaque in the coronary artery induces local thrombus formation which occludes coronary artery leading to myocardial infarction. Initially subendocardium is affected because this is the least supplied area. With continued ischemia the infarct zone extends through the subepicardial myocardium, producing a transmural Q wave myocardial infarction. Areas of myocardium which are ischemic but not yet undergone infarction can be salvaged by early reperfusion therapy.
- Microscopy shows coagulative necrosis of myocardial fibers that is ultimately followed by myocardial fibrosis.

Clinical Features

- In up to one-half of cases, a precipitating factor appears to be present before MI, such as vigorous physical exercise, emotional stress, or a medical or surgical illness.
- Patient usually presents with chest pain, located in the substernal region which frequently radiates to the neck, left shoulder, and left arm. Chest pain of MI is more severe than angina and lasts for more than 20 minutes. Patient may also have dizziness, syncope, dyspnea, and fatigue.
- Anginal "equivalents" such as dyspnea and epigastric discomfort may also occur.
- Examination may reveal diaphoresis, pale cool skin, tachycardia, a third and/or fourth heart sound, bilateral basal crepitations (due to pulmonary edema), and sometimes hypotension. A transient systolic murmur may be heard over the apex due to ischemic dysfunction of the mitral valve apparatus.

Investigations

Electrocardiogram

- Initial ECG may be normal. If normal, it should be repeated every 15 minutes. ECG shows ST elevation in MI. Complete heart block, bundle branch block and arrhythmias may be seen. ECG changes are seen in leads which correspond to the infarcted region of myocardium. The presence of new ST elevation >2 mm in chest leads and >1 mm in other leads suggests MI.

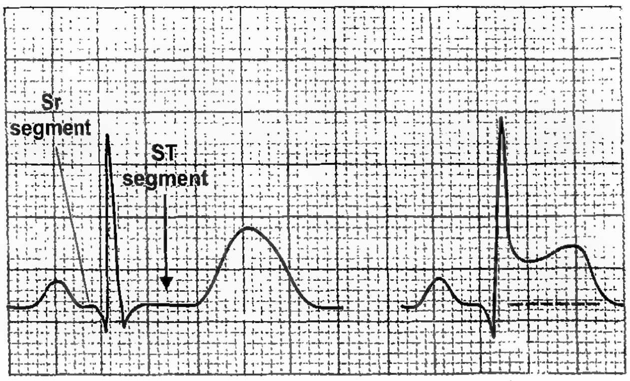

Fig. 3.7: Normal ECG (left) and abnormal ECG with ST elevation (right)

- ECG may show pathological Q waves after a few hours when the MI has evolved fully. Some patients may have only ST elevation and may not develop Q waves (non-Q wave MI). Presence of Q waves suggests that MI has fully evolved and there is full thickness infarct.
- New onset LBBB also suggests MI.

ECG leads showing ST-T changes	Correspond to
• V3, V4, V5, V6	• Anterior wall MI
• V2, V3	• Septal MI
• II, III, aVF	• Inferior wall MI
• I, aVL, V5, V6	• Lateral wall MI

Biochemical Markers

- CK-MB, troponin-I and troponin-T levels are elevated whenever there is myocardial injury (in STEMI and NSTEMI). Troponins are more specific for myocardial injury because elevated CK-MB levels may be found in skeletal muscle damage also. New markers are becoming available such as myeloperoxidase and glutathione peroxidase-1.

Echocardiogram

- Hypokinesia or akinesia of ventricular wall may be present due to ischemia or infarction. Echocardiogram can assess left ventricular (LV) function and also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. VSD and mitral regurgitation may develop in MI, which can be identified by echocardiogram.

Coronary Angiography (CAG)

- It can identify the site of block and allow percutaeous coronary intervention.

Radionuclide Imaging

- These imaging techniques are not used commonly because they lack sensitivity and specificity and are available in a few centers. Myocardial perfusion imaging with thallium-201 or technetium-99m sestamibi can show uptake defects (cold spots) due to infarction. Perfusion scanning cannot distinguish new infarcts from old infarcts. Radionuclide ventriculography, with technetium-99m-labeled red blood cells, can demonstrate wall motion disorders and reduction in the ventricular ejection fraction in MI.

Other Investigations

- Full blood count, renal function tests, serum electrolytes, glucose, and lipid profile should be done for all patients.

Management of Myocardial Infarction

Immediate Measures

- Note that time is muscle and treatment should be initiated as early as possible. More delay means more myocardial damage.
- Oxygen by nasal prongs or face mask (2–4 liters/min for 6–12 hours after infarction).
- Aspirin 300 mg oral and clopidogrel 300 mg oral loading dose should be given and continued at lower doses thereafter.
- Sublingual glyceryl trinitrate 0.4 mg. Repeat at 5-min intervals up to 3 doses. This relieves chest pain and improves coronary circulation.
- Intravenous heparin is given for all patients unless there is a contraindication.
- Injection morphine 2–5 mg intravenously, improves chest pain and controls anxiety.
- Intravenous beta blocker, e.g. metoprolol, 5 mg every 2 to 5 mins for a total of three doses. Beta blockers decrease heart rate and sympathetic overactivity and hence reduce myocardial oxygen demand. Beta blockers should be avoided if PR interval is >0.24 s, 2nd or 3rd degree atrioventricular block is present, heart rate is <60 beats/min, systolic blood pressure <90 mm Hg, history of asthma or COPD is present and severe left ventricular failure is present.

Reperfusion Therapy

- Coronary reperfusion can be established by two ways; (1) percutaneous coronary intervention (PCI) and (2) thrombolytic therapy.
- PCI is the treatment of choice if facilities for PCI are available. If there are no facilities for (PCI), the patient is treated with fibrinolytic therapy.
- Patients with continued chest pain or failure to resolve ST segment elevation by about 90 min after fibrinolysis should be referred for rescue PCI.
- Pre-hospital treatment, including thrombolysis, can be given by trained personnel under strict guidelines if there is going to be significant delay before reaching the hospital.

Fibrinolysis

- Fibrinolytic therapy reduces infarct size, limits LV dysfunction, and reduces the incidence of complications such as septal rupture, cardiogenic shock, and malignant ventricular arrhythmias.
- Highest benefit is obtained if fibrinolysis is done within 1 to 3 hours of the onset of symptoms. Modest benefit is seen if given 3 to 6 hours after the onset of infarction. Benefit may be seen up to 12 hours if chest pain is

persisting and ST segment remains elevated without Q waves. Fibrinolytic agents activate plasminogen to plasmin which breaks down the thrombus. Currently available fibrinolytic agents include streptokinase, tissue plasminogen activator (tPA), reteplase and tenecteplase.

- Streptokinase is given in a dose of 1.5 million units as intravenous infusion over 1 hour. tPA is given as 15 mg bolus IV followed by 0.75 mg/kg IV over 30 minutes followed by 0.5 mg/kg IV over the next 60 minutes. Streptokinase is not fibrin specific where as tPa is fibrin specific and hence associated with less chances of hemorrhage.
- Trials have shown that tissue plasminogen activator (tPA) plus heparin is better than streptokinase in improving survival as well as patency of coronary artery. Longer-acting variants of tPA, given by single (tenecteplase) or double bolus (reteplase) injections, have been developed and are more convenient to give.
- The major risk of thrombolytic therapy is bleeding. Intracerebral hemorrhage is the most serious and frequently fatal complication.
- Note that fibrinolysis is not useful in non-ST elevation, MI and may be harmful.

Table 3.24 Contraindications to thrombolysis

Absolute contraindications
- Hemorrhagic stroke or stroke of unknown origin at any time and ischemic stroke in preceding 6 months
- Intracranial or spinal cord neoplasms
- Active bleeding or bleeding diathesis
- Suspected or known aortic dissection

Relative contraindications
- Severe uncontrolled hypertension (systolic blood pressure >180 mm Hg)
- Recent major trauma/surgery/head injury (within preceding 3 weeks)
- Anticoagulation with INR >2–3
- Old ischemic stroke
- Oral anticoagulant therapy
- Pregnancy or within 1 week postpartum
- Recent non-compressible vascular punctures
- Recent retinal laser therapy

Percutaneous coronary intervention (PCI)

- PCI includes angioplasty and/or stenting. If PCI is done without preceding fibrinolysis, it is referred to as primary PCI. It is useful for patients who have contraindications to fibrinolytic therapy, when the diagnosis is in doubt, cardiogenic shock is present, increased bleeding risk is present, or symptoms have been present for at least 2 to 3 hours when the clot is more mature and fibrinolytics are less effective. Even if there are no contraindications, PCI can be a treatment option because it is more effective than fibrinolysis in opening occluded coronary arteries and has better short- and long-term clinical outcomes. Disadvantages of PCI are increased cost, limited availability and requirement of experts.

Coronary artery bypass grafting (CABG)

- CABG is indicated for patients with left main stem or triple vessel disease with impaired left ventricular function.

Complications of Myocardial Infarction

Heart Failure

- Cardiac failure can happen after MI if significant myocardium is damaged. The Killip classification is used to assess patients with heart failure post-MI.
  - *Killip I*: No crackles and no third heart sound
  - *Killip II*: Crackles in <50% of the lung fields or a third heart sound
  - *Killip III*: Crackles in >50% of the lung fields
  - *Killip IV*: Cardiogenic shock.
- Heart failure is treated with diuretics (furosemide or torsemide or spironolactone) which reduce blood volume and preload. Nitrates also reduce preload by venodilatation without reducing blood volume. Digoxin is a positive inotropic agent and helpful in severe heart failure.

Myocardial Rupture and Aneurysmal Dilatation

- Infarcted myocardium is weak and cannot tolerate the pressure inside the ventricular chamber. This may lead to rupture of the free wall of the left ventricle or aneurysmal dilatation. Rupture is usually an early, catastrophic and fatal event.
- Ventricular aneurysm impairs cardiac output because of paradoxical motion of its wall. Double, diffuse, or displaced apical impulse is noted on physical examination.

Ventricular Septal Defect (VSD)

- Infarcted septum may perforate and lead to VSD. It is common in elderly and hypertensive patients and after delayed thrombolysis. It requires emergency surgical repair.

Mitral Regurgitation

- Severe mitral regurgitation can occur early in the course of MI. Three mechanisms are responsible for mitral regurgitation in MI, which are as follows:
  - Left ventricular dysfunction and dilatation, causing annular dilatation of the valve and subsequent regurgitation.

- Infarction of the inferior wall, producing dysfunction of the papillary muscle.
- Infarction and rupture of the papillary muscles, producing sudden severe mitral regurgitation, pulmonary edema and cardiogenic shock.
- If there is rupture of papillary muscles, emergency surgery should be undertaken.

Cardiac Arrhythmias

- ***Ventricular tachycardia and ventricular fibrillation (VT and VF)***: Both are common after MI, especially after reperfusion therapy. VF is a common cause of death after MI in first 24 hours. Hemodynamically unstable (hypotension, cyanosis) VT and VF should be treated with DC shock. Hemodynamically stable VT should be treated with intravenous beta blockers (metoprolol, esmolol), IV lidocaine, or IV amiodarone. Refractory VT and VF may respond to IV magnesium sulphate.
- ***Atrial fibrillation***: It is common after MI and can be treated with beta blockers and digoxin. DC shock may also be given provided there is no clot in the heart. Intravenous diltiazem or verapamil can be used if there is any contraindication to β blocker use. Amiodarone can be used daily to prevent recurrence.
- ***Bradyarrhythmias***: These are common following MI and may be due to sinus node dysfunction and conduction disturbances. AV block may occur during acute MI, especially after inferior wall MI (the right coronary artery usually supplies the SA and AV nodes). Heart block, with hemodynamic compromise (hypotension) requires treatment with atropine or a temporary pacemaker. AV blocks are usually transient and recover later. Permanent pacemaker may be needed if they persist even after 2 weeks.

Acute Pericarditis

- It happens with large, "transmural" infarctions causing pericardial inflammation and presents on days 2 to 4 after MI. pericardial effusion may devlop and cause tamponade. Pericarditis developing later (2 to 10 weeks) after acute MI may represent ***Dressler's syndrome***, which is immune-mediated. Treatment includes aspirin or other NSAIDs (indomethacin). Corticosteroids may be required for severe pericarditis.

Post-MI Drug Therapy

- Extensive clinical trials have shown that many drugs taken indefinitely by MI patients reduce the incidence of recurrent MI and cardiovascular death. Therefore, all post-MI patients should be taking the following medications unless there are contraindications.
- ***Aspirin and clopidogrel***: Should be given to all patients lifelong. Aspirin is given at a dose of 75–150 mg/day and clopidogrel at 75 mg/day.
- ***Beta blocker***, e.g. metoprolol, carvedilol, atenolol. They decrease myocardial oxygen demand and should be given to all patients with MI unless there is a contraindication like asthma or severe LV dysfunction.
- ***Oral nitrates***, e.g. isosorbide dinitrate or mononitrate. They improve the symptoms of angina and heart failure and should be considered for all patients.
- ***ACE inhibitors***, e.g. enalapril, ramipril, lisinopril, perindopril. They prevent adverse myocardial remodeling after acute MI and reduce heart failure and death. They also reduce atherosclerosis progression and acute MI recurrence. All patients should be given ACE inhibitor unless there is a contraindication like renal failure and hypotension.
- ***Statins***, e.g. atorvastatin, rosuvastatin, etc. LDL cholesterol should be brought down to less than 100 mg/dl. In addition to cholesterol lowering effect, statins also help in plaque stabilization and regression of atherosclerosis. Recent data show statins are effective in *secondary* prevention regardless of age or baseline lipid levels, even when the LDL is less than 100.
- ***Control of comorbid conditions***: Like diabetes and hypertension help in reducing recurrent MI. For HTN, ACE inhibitors or β blockers are the first choice because they also reduce cardiovascular mortality and morbidity as described above. Angiotensin receptor blockers (ARBs) can be considered when ACE inhibitors are not tolerated. ACE inhibitors and ARBs also reduce the long-term complications of diabetes. Diabetes should be strictly controlled by oral drugs or insulin or both.
- ***Calcium channel blockers***: They have negative inotropic effect and are not routinely given. They may be given to selected patients without LV dysfunction (ejection fraction greater than 40%) who are intolerant of β blockers. Short acting nifedipine should be avoided as it cause reflex tachycardia has been shown to increase mortality rate.
- ***Smoking cessation***: Continued smoking doubles subsequent mortality risk after acute MI and cessation reduces risk of reinfarction and death.

Post-MI assessment

- Patients, in whom primary angioplasty has not been performed, need to undergo exercise test to identify residual ischemia and to determine the need for coronary angiography. This can be done prior to discharge in patients without angina or 6 weeks later. A positive test requires diagnostic/therapeutic coronary angiography/

stenting. Alternatively, nuclear scintigraphy or dobutamine stress echocardiography can be used at 5 days to determine the amount of viable myocardium and the extent of myocardial ischemia.

Q. Cardiogenic shock.

- Cardiogenic shock is a state of inadequate tissue perfusion due to cardiac dysfunction.

Etiology

Table 3.25 Causes of cardiogenic shock

• Acute MI (most common cause)	• End stage cardiomyopathy
• Acute mitral regurgitation	• Severe myocarditis
• Acute aortic regurgitation	• Left ventricular free wall rupture
• Acute ventricular septal defect due to rupture of interventricular septum	• Pericardial tamponade

Clinical Features

- Sinus tachycardia.
- Severe systemic hypotension (systemic hypotension is defined as a persistent systolic blood pressure below 80 mm Hg or a mean blood pressure 30 mm Hg lower than the patient's baseline level). This is due to acute decrease in stroke volume.
- Signs of systemic hypoperfusion (e.g. cool extremities, oliguria).
- Dyspnea due to pulmonary congestion.

Differential Diagnosis

- Hemorrhagic shock.
- Septic shock.

Investigations

- ***ECG*** may show acute MI or other causes of cardiogenic shock.
- ***Echocardiography*:** It can assess ventricular function, detect tamponade, severe mitral and aortic regurgitation, and ventricular septal rupture.
- ***Coronary angiography*:** To assess the coronary anatomy should be performed in all patients with cardiogenic shock who are candidates for percutaneous coronary intervention or coronary artery bypass graft surgery.

Management

General Measures

- Admit in ICU
- Strict bed rest
- High flow oxygen
- Endotracheal intubation and mechanical ventilation if required.

Circulatory Support

Pharmacologic Agents

- Dopamine or norepinephrine infusion or both can used to correct hypotension. Amrinone or milrinone infusion can be used if there is myocardial pump failure. Dobutamine should be used cautiously in the presence of hypotension as it has peripheral vasodilating action.

Mechanical Devices

- IABP (intra-aortic balloon pump) can produce rapid, although temporary, stabilization of the patient with cardiogenic shock. It is usually inserted through the femoral artery and placed in the descending thoracic aorta distal to the left subclavian artery. The balloon inflates during diastole and deflates during systole (in a synchronous fashion with the cardiac cycle), resulting in diastolic blood flow augmentation and systolic reduction in afterload. The decline in afterload is due to a brief vacuum effect created by rapid balloon deflation.
- Other circulatory support devices are left ventricular and biventricular assist devices and percutaneous cardiopulmonary bypass support with use of an extracorporeal membrane oxygenator.

Temporary Biventricular Pacing

- May help improve the symptoms and survival of cardiogenic shock.

Treatment of Underlying Cause

- Underlying cause such as acute MI, acute mitral and aortic regurgitations, etc. require specific therapy.

Q. Sudden cardiac death.

Definition

- Sudden cardiac death (SCD) is death due to instantaneous, unanticipated circulatory collapse due to cardiac causes within 1 hour of initial symptoms.
- SCD has a circadian pattern with a peak in the morning hours after awakening, from 6 AM to 12 noon. This peak may be due to a surge in sympathetic activity with its attendant arrhythmogenic effects.

Etiology

- Most of the time it is due to cardiac arrhythmias (ventricular tachycardia and ventricular fibrillation) or asystole.

- It is more common in men.
- Pre-existing heart disease may or may not to be present, but the time and mode of death are unexpected. Risk factors for SCD are identical to those for coronary artery disease and include age, male gender, hypertension, tobacco use, hypercholesterolemia, and left ventricular hypertrophy.

Cardiac diseases associated with sudden cardiac death

- Ischemic heart disease
- Cardiomyopathies
- Congenital long QT syndrome
- Brugada's syndrome
- Cardiac failure
- Acute myocarditis
- Valvular heart disease (aortic stenosis, mitral valve prolapse)
- Congenital heart disease (tetralogy of Fallot, transposition of great arteries, VSD, PDA)

Clinical Features

- Patients at risk for SCD may have prodromes of chest pain, fatigue, palpitations, and other nonspecific complaints.
- The physical examination may reveal evidence of underlying myocardial disease or may be entirely normal.

Investigations

- ***ECG:*** Should be done in all patients. Evidence of MI, prolonged QT interval, short QT interval, epsilon wave, short PR interval, a WPW pattern, or other conditions should be sought.
- ***Echocardiogram*:** May show evidence of underlying heart disease.
- ***Cardiac enzymes (CK-MB, troponins)*:** Elevations in these enzyme levels may indicate acute coronary syndrome.
- ***Electrolytes, calcium, and magnesium*:** Severe metabolic acidosis, hypokalemia, hyperkalemia, hypocalcemia, and hypomagnesemia are some of the conditions that can increase the risk for arrhythmia and sudden death.
- ***Quantitative drug levels (quinidine, procainamide, tricyclic antidepressants, digoxin)*:** Drug levels higher than the levels indicated in the therapeutic index may have a proarrhythmic effect. Subtherapeutic levels of these drugs in patients being treated for specific cardiac conditions also can lead to an increased risk for arrhythmia. Most of the antiarrhythmic medications also have a proarrhythmic effect.
- ***Toxicology screen*:** Drugs such as cocaine can lead to vasospasm-induced ischemia.
- ***Thyroid function tests*:** Hyperthyroidism can lead to tachycardia and tachyarrhythmias. Over a period, it also can lead to heart failure. Hypothyroidism can lead to QT prolongation.
- ***Brain natriuretic peptide (BNP)*:** Raised level indicates cardiac failure.

Treatment

- Immediate cardiopulmonary resuscitation should be started for cardiac arrest. Immediate defibrillation is very important for a good outcome.
- An implantable cardioverter-defibrillator (ICD) prevents sudden death due to ventricular arrhythmias and cardiac arrest in people with high risk.
- Antiarrhythmic drugs such as amiodarone may be used as an alternative to an implantable cardioverter-defibrillator but are less effective.
- Beta blockers, ACE inhibitors and spironolactone have been shown to reduce the risk of sudden cardiac death.

Q. Define cardiac arrest. Discuss the causes and management of cardiac arrest.

Q. Cardiopulmonary resuscitation (CPR).

- Cardiac arrest is defined as sudden loss of pumping ability of the heart. This leads to abrupt loss of consciousness due to lack of cerebral blood flow. It leads to death in the absence of an active intervention, although spontaneous reversions occur rarely.
- Cardiac arrest occurring in hospital has better chances of survival than out of hospital arrest. Similarly cardiac arrest due to VT or VF has better chances of survival than cardiac arrest due to asystole and pulseless electrical activity.
- The onset of irreversible brain damage usually begins within 4 to 6 minutes after loss of cerebral circulation.

Causes of Cardiac Arrest

- VF (ventricular fibrillation)
- VT (ventricular tachycardia)
- Asystole
- Pulseless electrical activity
- Rupture of the ventricle
- Cardiac tamponade
- Massive pulmonary embolism
- Acute disruption of a major blood vessel.
- Myocardial infarction
- Electrolyte imbalance (hypkalemia and hyperkalemia)
- Drugs

Management of Cardiac Arrest (Cardiopulmonary Resuscitation)

- The most important thing which increases the survival after cardiac arrest is immediate CPR. The sooner it is initiated the better is the prognosis.
- The goals of CPR in cardiac arrest are (1) restoring a spontaneous circulation as quickly as possible; and (2) maintaining continuous artificial circulatory support until return of a spontaneous circulation has been achieved.
- The keys to survival from sudden cardiac arrest are early recognition, early CPR, early defibrillation and early transfer to hospital.
- *CPR consists of 4 main parts*:
  1. Circulation (C)
  2. Airway (A)
  3. Breathing (B)
  4. Defibrillation (D)
- Note that as per new American Heart Association guidelines, the sequence of CPR is CAB and not ABC. The management strategy for cardiac arrest can be divided into five steps:
  1. Initial assessment and activation of emergency medical services
  2. Basic life support (BLS)
  3. Early defibrillation by a first responder (if available)
  4. Advanced life support (ALS)
  5. Post-resuscitation care.

Initial Assessment and Activation of Emergency Medical Services

- Assess the victim for response. If no response, call for help. If you are alone activate emergency services and get an automatic external defibrillator if available.

BLS

- Check for pulse. This is best done by feeling for carotid pulse at the neck. You should take at least 5 seconds and no more than 10 seconds to assess pulse.
- If there is no carotid pulse, chest compressions should be started at a rate of 100/minute. Chest should be compressed in the middle of chest at the level of nipple line.
- Open the victim's airway and check for breathing. Airway can be opened by head tilt-chin lift manuere.
- If there is no breathing, give 2 breaths (either mouth to mouth or by using a face mask). The breaths should make the chest rise and fall.
- This cycle of 30 compressions and 2 breaths should be continued until the return of spontaneous circulation and breathing or till the patient is declared dead. Breaths can be given by mouth to mouth breathing or by using bag and mask device. Patient can also be intubated using endotracheal tube for more effective ventilations.

Early Defibrillation by a First Responder

- Since the terminal event in most cases of cardiac arrest is ventricular fibrillation, defibrillation as early as possible is very important for successful resuscitation of the victim. For this purpose, automated external defibrillators (AED) can be made use of in a setting outside the hospital. Such AEDs are kept at public places such as airports, railway stations, shopping malls, etc. AED can be used even by lay people.

Advanced Life Support (ALS)

- This involves use of various drugs during CPR such as injection adrenaline (1 mg of 1:10,000 solution) and atropine (1 mg). These drugs are given intravenously. Adrenaline can be repeated many times. Atropine can be given up to three times. Other drugs which are useful in cardiac arrest are calcium gluconate, sodium bicarbonate, magnesium sulphate (2 gm IV for torsade de pointes), and amiodarone (for ventricular tachycardia). Bag-mask ventilation or endotracheal intubation is done for maintaining airway and breathing. Manual defibrillators are used inside the hospital for defibrillation because the rescuer needs to have knowledge of advanced life support and ECG interpretation skills.

Post-resuscitation Care

- After revival, patient should be kept in recovery position and monitored in ICU. The cause of cardiac arrest should be established and treated.

Q. Cardioversion and defibrillation.

- Cardioversion is the delivery of electrical shock that is synchronized to the R wave of QRS complex, while defibrillation is nonsynchronized delivery of shock (delivered randomly during the cardiac cycle). The machine used for cardioversion and defibrillation is called defibrillator.
- During defibrillation and cardioversion, electrical current travels from the negative to the positive electrode by traversing myocardium. It causes all of the heart cells to contract simultaneously. This interrupts and terminates abnormal electrical rhythm. This, in turn, allows the sinus node to resume normal pacemaker activity.
- Old defibrillators delivered energy in a monophasic waveform, meaning that electrons flowed in a single direction. Latest defibrillators deliver a biphasic waveform. Biphasic defibrillators successfully terminate arrhythmias at lower energies than monophasic defibrillators.

Indications

- Atrial fibrillation
- Atrial flutter
- Supraventricular tachycardia
- VT (ventricular tachycardia)
- VF (ventricular fibrillation).

Precautions

- Patient should be anesthetized or sedated before elective cardioversion. This does not apply to emergency situations.
- Patients with chronic atrial fibrillation should be anticoagulated for 6 weeks before elective cardioversion.

Method

- There are two electrodes in the defibrillator. One is applied below the right clavicle. Another is applied on the lower part of left axilla. Required amount of energy is selected. After clearing everybody from the patient, shock is delivered by pressing the shock button.

Complications

- ECG changes (ST segment and T wave changes).
- Precipitation of new arrhythmias.
- Embolization (pulmonary or systemic embolization). This complication is more likely to occur in patients with AF who have not been anticoagulated prior to cardioversion.
- Myocardial dysfunction and necrosis.
- Transient hypotension.
- Pulmonary edema.
- Skin burns.

Q. Define and enumerate the causes of left ventricular hypertrophy (LVH) and LV dilatation.

- LVH is defined as an increase in the mass of the left ventricle, due to increase in wall thickness.
- Left ventricular dilatation refers to increase in cavity size.

Causes of LVH

- Hypertension
- Aortic stenosis
- Coarctation of the aorta
- Hypertrophic obstructive cardiomyopathy

Causes of Left Ventricular Dilatation

- Aortic regurgitation
- Mitral regurgitation
- VSD
- PDA
- Dilated cardiomyopathy
- Myocardial infarction
- Cardiac failure
- Hyperkinetic circulatory states (anemia, thyrotoxicosis, beriberi, AV fistula)

Q. Discuss the etiology, clinical features, investigations, and management of acute rheumatic fever.

Q. Aschoff nodule.

Q. Erythema marginatum.

Q. Rheumatic chorea (Sydenham's chorea; St. Vitus Dance).

Q. Jones criteria.

Q. Rheumatic fever prophylaxis.

Definition

- Rheumatic fever is an autoimmune inflammatory process that develops as a sequela of group A beta-hemolytic Streptococcus infection.
- Rheumatic fever involves the heart, joints, central nervous system, skin, and subcutaneous tissues with varying frequency. Involvement of the heart, though rarely fatal during the acute stage, may lead to rheumatic valvular disease, which can lead to cardiac disability or death many years after the initial event.

Etiology

- Rheumatic fever follows pharyngeal infection with group A beta-hemolytic Streptococcus. It usually occurs two to three weeks after the attack of pharyngitis. However, at least one-third of patients deny previous sore throat, and cultures of the pharynx are often negative for group A streptococci at the onset of rheumatic fever. However, antibody response against Streptococcus can be demonstrated in almost all the cases.
- Skin infections are not associated with rheumatic fever but they can cause post-streptococcal glomerulonephritis.
- The serotypes causing rheumatic fever (rheumatogenic strains) are types 3, 5, 6, 14, 18, 19, and 24.

Epidemiology

- Rheumatic fever is a major health problem in the developing countries of Asia, Africa, the Middle East, and Latin America.
- The incidence of rheumatic fever has decreased now because of the availability of antibiotics.

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- Outbreaks of rheumatic fever closely follow epidemics of streptococcal pharyngitis or scarlet fever with associated pharyngitis. Patients who have suffered an initial attack tend to experience recurrences of the disease following group A streptococcal infections. Adequate treatment of streptococcal pharyngitis markedly reduces the incidence of rheumatic fever. Recurrence is rare beyond age 34.
- Acute rheumatic fever is most common among children in the 5 to 15-year age group. There is no clear-cut sex predilection, although there is a female preponderance in rheumatic mitral stenosis and in Sydenham's chorea.

Pathogenesis

- Molecular mimicry is thought to play an important role in tissue injury. There are shared epitopes between cardiac myosin and streptococcal M protein that lead to cross-reactive humoral and T cell immunity against group A streptococci and the heart. Epitopes of streptococcal M protein also share antigenic determinants with heart valves, sarcolemmal membrane proteins, synovium, and articular cartilage. Circulating antibodies against group A streptococcal cell membranes which cross react with neurons of the caudate and subthalamic nuclei have been found in children with Sydenham's chorea.
- Host factors may also play a role. Associations between disease and human leukocyte antigen (HLA) class II alleles have been identified. Certain B cell alloantigens are expressed to a greater level in patients with rheumatic fever.
- During active rheumatic carditis, there is T cell and macrophage infiltration of heart valves, and the production of interleukin-1 and interleukin-2 is increased. All these result in scarring and collagen deposition in the valves and destruction of myocytes. There will be exudative and proliferative inflammatory lesions in the connective tissue of the heart, joints, and subcutaneous tissue. All the three layers of the heart are involved (pancarditis).

Pericardium

- Pericarditis is common and fibrinous pericarditis is occasionally present. Thick exudates gives bread and butter appearance macroscopically. Pericarditis usually heals without any sequelae. Tamponade is rare.

Myocardium

- In the myocardium, there is fragmentation of collagen fibers, lymphocytic infiltration, fibrinoid degeneration and the presence of Aschoff nodules, which are considered pathognomonic of acute rheumatic fever.
- The Aschoff nodule consists of an area of central necrosis surrounded by lymphocytes, plasma cells, and large mononuclear and giant multinucleate cells. Many of these cells have an elongated nucleus with a clear area just within the nuclear membrane ("owl-eyed nucleus").
- Aschoff nodules may also be found in endomyocardial biopsy specimens obtained from patients with acute rheumatic carditis.

Endocardium

- Endocarditis is responsible for chronic rheumatic valvulitis. Small vegetations, 1 to 2 mm in diameter, are seen on the atrial surface of valve margins and chordae tendinea. There is edema and inflammation of the valve leaflets.
- A thickened and fibrotic patch (MacCallum's patch) may be found in the posterior left atrial wall. It is believed to be due to mitral regurgitant jet impinging on the left atrial wall.
- Healing of the valvulitis leads to fibrosis of the leaflets and fusion of the chordae resulting in valvular stenosis or incompetence.
- The mitral valve is affected most commonly, followed by the aortic valve. Tricuspid and pulmonic valves are rarely affected.

Extracardiac Lesions

- Inflammation can affect the joints (rheumatic arthritis). skin (subcutaneous nodules), lung (rheumatic pneumonitis) and brain.

Clinical Features

General

- High fever, lassitude, prostration, tachycardia. Fever is usually low-grade and rarely lasts for more than 3 to 4 weeks.

Sore Throat

- Only two-thirds of patients give history of preceding sore throat.

Cardiac

- Carditis occurs in 40 to 50% of patients with rheumatic fever. Carditis usually occurs within the first 3 weeks of the illness.
- Carditis is the only manifestation of acute rheumatic fever that has the potential to cause long-term disability and death. Cardiac failure can occur due to severe mitral regurgitation or severe myocarditis.
- It involves all the three layers of the heart, i.e. endocardium, myocardium and pericardium.

Endocarditis

- Valvulitis is associated with characteristic murmurs.
- Mitral regurgitation produces a pansystolic murmur best heard at the apex and radiating to the axilla.
- Increased flow across the mitral valve in the presence of valvulitis may produce a mid-diastolic murmur (Carey Coombs' murmur). Carey-Coombs' murmur can be differentiated from the diastolic murmur of mitral stenosis by the absence of an opening snap, presystolic accentuation, and loud first sound.
- Aortic regurgitation produces a high-pitched decrescendo early diastolic murmur.

Myocarditis

- Inappropriate tachycardia
- S3, S4, or summation gallops may be audible.
- Cardiomegaly.
- Acute congestive heart failure can develop leading to hepatic congestion and right upper quadrant pain and tenderness. Congestive heart failure is usually caused by left ventricular volume overload associated with severe mitral or aortic regurgitation.

Pericarditis

- Pericardial friction rub
- Muffled heart sounds due to pericardial effusion. Large effusions leading to tamponade are rare.

Polyarthritis

- Arthritis is the most frequent major manifestation of rheumatic fever (occurs in approximately 75% of patients). Arthralgia is pain in the joints without signs of inflammation.
- It is migratory polyarthritis (joints are involved in quick succession, and each for a brief period of time).
- Usually larger joints such as knees, ankles, elbows, and wrists are involved.
- Small joints and spine are involved rarely.
- Polyarthritis responds dramatically to salicylate therapy.
- Inflammation of any one joint subsides spontaneously within a week and the entire bout of polyathritis rarely lasts more than 4 weeks. Resolution is complete with no residual deformity. However, rarely Jaccoud deformity of the metacarpophalangeal joints can occur after repeated attacks of rheumatic fever. This is a periarticular fibrosis and not a true synovitis.

Subcutaneous Nodules

- It occurs in less than 10% of patients. These are usually associated with carditis and isolated occurrence of nodules is rare.
- They are round, firm, painless, freely movable subcutaneous lesions varying in size from 0.5 to 2 cm.
- Common sites of occurrence are over bony surfaces and over tendons such as elbows, knees, and wrists, the occiput and vertebrae.
- They last for 1 to 2 weeks and disappear spontaneously.
- Similar nodules also occur in rheumatoid arthritis and SLE.

Erythema Marginatum

- It occurs in less than 10% of patients. This rash is usually found on the trunk and proximal parts of the extremities. Face is spared.
- It appears as erythematous macule or papule with clear center. Lesions may merge and form serpiginous patterns.
- They are not pruritic, nonindurated and blanch on pressure.
- The rash is transient, migrating from place to place without leaving residual scarring. Erythema marginatum has also been reported in sepsis, drug reactions, and glomerulonephritis.

Chorea (Sydenham's chorea; St. Vitus Dance)

- It occurs in 15% of rheumatic fever cases. It can occur in isolation, several months after the attack of rheumatic fever.
- It is most common in the age group of 7 to 14 years and is rare after puberty.
- It is characterized by rapid, purposeless, involuntary movements, most noticeable in the extremities and face. The speech is usually slurred and jerky.
- The involuntary movements disappear during sleep and may be suppressed by sedation. Emotional lability is characteristic of Sydenham's chorea and may often precede other neurologic manifestations.
- Most patients recover in 6 months.

Other Clinical Features

- Abdominal pain in rheumatic fever is due to peritoneal inflammation and may be confused with acute appendicitis or sickle cell crisis.
- Epistaxis has been reported in some patients.

Jones Criteria for the Diagnosis of the Initial Attack of Rheumatic Fever

- The presence of two major manifestations or one major and two minor manifestations indicates a high probability of acute rheumatic fever.

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Table 3.26 Jones criteria

Major manifestations	Minor manifestations
• Carditis • Polyarthritis • Chorea • Erythema marginatum • Subcutaneous nodules	• Arthralgia • Fever • Elevated ESR or CRP level • Prolonged PR interval • Evidence of preceding group A streptococcal infection—positive throat culture or rapid antigen test result • Elevated or rising streptococcal antibody titer

Differential Diagnosis

- Rheumatic fever may be confused with the following:
  - Rheumatoid arthritis
  - Osteomyelitis
  - Infective endocarditis
  - Chronic meningococcemia
  - SLE
  - Lyme disease
  - Sickle cell anemia

Laboratory Findings

General Tests

- Mild to moderate normochromic normocytic anemia
- Polymorphonuclear leukocytosis
- Elevated CRP and ESR are usually present.

Evidence of Preceding Streptococcal Infection

- Throat cultures are usually negative for group A streptococci by the time rheumatic fever appears.
- Streptococcal antibody tests (antistreptolysin O (ASO), anti-DNAse B, antihyaluronidase and antistreptozyme test). ASO titre is elevated in 80 percent or more of patients with rheumatic fever. ASO titers greater than 200 Todd units/ml in adults and 320 Todd units in children are considered elevated. Rising titers are more significant than a single test. Antistreptozyme test (ASTZ) is a very sensitive test for recent streptococcal infection. Titres of more than 200 units/ml are positive. ASTZ is more useful to rule out rheumatic fever.

ECG

- Persistent sinus tachycardia that does not resolve during sleep is common in carditis. Prolongation of the PR interval is a consistent finding.
- AV conduction abnormalities, atrial flutter and fibrillation can occur due to carditis.
- Low QRS voltage may be noted if a large pericardial effusion is present.

Echocardiogram

- Rheumatic mitral valvulitis associated with annular dilation and elongation of the chordae to the anterior leaflet, resulting in mitral regurgitation.
- Valvular thickening and the presence of nodular lesions on the body and tips of the mitral leaflet have been described.
- Heart failure.

Endomyocardial Biopsy

- It has limited role in the diagnosis of rheumatic fever. Presence of Aschoff nodules, interstitial mononuclear infiltrates with or without myocyte necrosis is seen in biopsy specimens. Biopsy can be done by percutaneous transvenous route.

Treatment

Management of Acute Episode of Rheumatic Fever

- The patient should be kept at strict bed rest until the fever subsides, and ESR, pulse rate, ECG have all returned to baseline.
- ***Antibiotics***: Although evidence of active infection is unusual during the acute phase, it is recommended that patients receive a single dose of benzathine penicillin or a 10-day course of penicillin-V (or erythromycin if penicillin allergic) to curtail exposure to streptococcal antigens. After completion of the course, secondary prophylaxis should be commenced.
- ***Anti-inflammatory drugs***: They provide symptomatic relief of fever, and joint pain. They are not curative and do not prevent the development of rheumatic heart disease. Aspirin is very effective for fever and joint inflammation. Corticosteroids are used in patients with carditis manifest by heart failure and in patients who do not tolerate aspirin. Prednisone 40 to 60 mg per day is given for 2 to 3 weeks and then gradually tapered over the next 3 weeks. There is limited experience with other NSAIDs.
- Cardiac failure is managed by diuretics, ACE inhibitors, and beta blockers. Digoxin should be used cautiously in the presence of myocarditis. Mitral valve repair or replacement may be life-saving in acute intractable heart failure.

Prevention of Rheumatic Fever

- ***Primary prevention***: Primary prevention refers to antibiotic treatment of group A streptococcal pharyngitis to prevent the first attack of acute rheumatic fever. All

attacks of streptococcal pharyngitis should be treated adequately with antibiotics using penicllins or erythromycin. An outbreak of rheumatic fever in a closed population should be controlled by mass pencillin prophylaxis.

- *Secondary prevention (rheumatic fever prophylaxis)*: Patients who have already suffered an attack of rheumatic fever are at risk of developing recurrent attacks of rheumatic fever. Recurrent attacks lead to progressive cardiac damage. Hence, rheumatic fever patients should be protected from subsequent streptococcal infections by giving continuous antimicrobial prophylaxis. The risk of reccurence decreases as the age advances.

Drugs Used for Prophylaxis

Benzathine penicillin G 1.2 million units deep IM (buttocks) every month. However, injections every three weeks may be more effective in preventing recurrences of acute rheumatic fever.

OR

Penicillin V 250 mg twice daily oral (for patients who cannot be given IM injection such as patients on anti-coagulation).

OR

Erythromycin 250 mg twice daily oral for patients who are allergic to penicillin.

The WHO recommendations for the duration of secondary prophylaxis are:

- Rheumatic fever with carditis and clinically significant residual heart disease requires antibiotic treatment for a minimum of 10 years after the latest episode; prophylaxis is required until the patient is aged at least 40–45 years and is often continued for life.
- Rheumatic fever with carditis and no residual heart disease aside from mild mitral regurgitation requires antibiotic treatment for 10 years or until age 25 years (whichever is longer).
- Rheumatic fever without carditis requires antibiotic treatment for 5 years or until the patient is aged 18–21 years (whichever is longer).

Q. Discuss the etiology, clinical features, investigations, complications, and management of mitral stenosis.

- In normal adults, the cross-sectional area of the mitral valve orifice is 4 to 6 cm^2. If the orifice is reduced to less than this, it is called mitral stenosis.
- Usually patients will not experience any symptoms until the valve area is reduced to les than 2.5 cm^2. Mitral stenosis is considered mild when valve area is 2.5 to 1.5 cm^2, moderate when 1.5 to 1 cm^2, and severe or critical when less than 1.0 cm^2.

Etiology

Table 3.27 Etiology of mitral stenosis

• Rheumatic heart disease	• Rheumatoid arthritis
• Congenital mitral stenosis	• Mucopolysaccharidoses (Hurler's syndrome)
• Carcinoid tumors	• Gout
• Amyloidosis	• Fabry disease
• Systemic lupus erythematosus	• Whipple disease

- Rheumatic heart disease is the most common cause of MS, but only 50% patients remember the attack of rheumatic fever. MS is the most common valve lesion due to rheumatic fever. Rheumatic mitral stenosis is more common in women.

Pathophysiology

- When there is mitral stenosis, blood from left atrium cannot flow easily into left ventricle. Hence, blood collects in the left atrium and pressure increases in the left atrium. Because of increased pressure, left atrial hypertrophy and dilatation occur.
- Due to increased left atrial pressure, pulmonary venous, pulmonary arterial and right heart pressures also increase. Increase in pulmonary vascular pressure leads to pulmonary edema and pulmonary hypertension.
- Pulmonary hypertension leads to right ventricular hypertrophy, dilatation and failure. Right ventricular dilatation results in tricuspid regurgitation.
- An increase in heart rate shortens diastole and hence the time available for ventricular filling. In the presence of MS (in which already there is problem with ventricular filling due to stenosis), any increase in heart rate reduces ventricular filling and raises left atrial pressure.

Clinical Features

History

- Patients are usually asymptomatic until the valve orifice is moderately stenosed. Patient gradually becomes symptomatic as the severity of mitral stenosis increases. The latent period between the initial attack of rheumatic carditis and the development of symptoms due to MS is generally about 20 years. Once the patient becomes seriously symptomatic, death occurs in 2 to 5 years unless the stenosis is corrected.
- Patients c/o dyspnea due to pulmonary venous congestion and development of pulmonary hypertension. Dyspnea is exertional initially, but as the severity of MS increases, it may be present at rest also.

- Orthopnea and paroxysmal nocturnal dyspnea can occur because of increased venous return in supine position and consequent congestion of pulmonary vasculature.
- Recurrent lower respiratory infections are common. A cough productive of blood-tinged, frothy sputum is common.
- When RV failure occurs, ascites and edema develop.
- Dilated left atrium may lead to atrial fibrillation, giving rise to symptoms such as palpitations. Atrial fibrillation may result in left atrial clot formation and systemic emboli, most commonly to the cerebral vessels resulting in stroke.

Physical Examination

- Patients may have a typical look called "mitral facies" or malar flush. This is a bilateral, cyanotic or dusky pink discoloration over the cheeks due to arteriovenous anastomoses and vascular stasis.
- Pulse is low volume and may be irregularly irregular due to atrial fibrillation.
- When right heart failure develops, there may be jugular venous distension, ascites, and pedal edema. Prominent a wave may be noted in JVP due to pulmonary HTN provided there is no atrial fibrillation.
- Cardiac apex is tapping in nature due to palpable first heart sound.
- Parasternal heave may be present due to right ventricular hypertrophy.
- Loud first heart sound and opening snap may be heard on auscultation. P_2 component of S_2 may be loud due to pulmonary HTN. A low-pitched mid-diastolic 'rumbling' murmur is heard with the bell of the stethoscope over the apex with the patient lying on the left side. Murmur becomes louder at the end of diastole as a result of atrial contraction (presystolic accentuation). Presystolic accentuation is absent in atrial fibrillation due to loss of atrial contraction.
- An opening snap may precede the middiastolic murmur. The gap between S_2 and the opening snap provides an estimation of the severity of the mitral stenosis. More severe MS causes higher left atrial pressure. Higher left atrial pressure makes the mitral valve open earlier (i.e. immediately after S_2). Hence, mitral valve opening snap becomes closer to S_2. More severe the MS, lesser the gap between S_2 and opening snap. Other findings which indicate the severity of MS are presence of pulmonary hypertension (implies severe mitral stenosis), and length of the mid-diastolic murmur which is proportional to the severity of MS. when the valve cusps become immobile, the loud first heart sound softens and the opening snap disappears.
- Pulmonary hypertension can cause pulmonary valvular regurgitation resulting in an early diastolic murmur in the pulmonary area known as Graham Steell's murmur.
- Other findings include, tender hepatomegaly, pleural effusions due to right heart failure.

Complications of Mitral Stenosis

- Atrial fibrillation with clot formation and systemic embolization
- Pulmonary hypertension and right heart failure
- Recurrent chest infections
- Hemoptysis
- Dysphagia due to esophageal compression by the enlarged left atrium
- Infective endocarditis (rare)

Investigations

Chest X-ray

- Chest X-ray shows left atrial enlargement, which produces straightening of the left heart border and a double density at the right heart border due to combined shadows of the right atrium and left atrium. Increased pulmonary vascularity is seen due to pulmonary venous hypertension. Kerley B lines, which represent distended interlobular septa and lymphatics, may be seen due to pulmonary venous engorgement. Calcified mitral valve may be visible in advanced MS.

Electrocardiogram

- ECG usually shows a bifid P wave due to left atrial enlargement and consequent delayed activation. Atrial fibrillation is frequently present. If pulmonary hypertension has developed, there may be features of right ventricular hypertrophy (right axis deviation and tall R waves in lead V_1).

Echocardiogram

- This is the most important tool to diagnose and confirm MS. It can assess the mitral valve apparatus, calculate mitral valve area, left atrial and right ventricular size and function. Estimation of pulmonary artery pressure can be made through measurement of the degree of tricuspid regurgitation. In most cases, echocardiography is enough to judge the severity of mitral stenosis and to make decisions regarding surgery.

Cardiac Catheterization

- This is required only if coexisting coronary artery disease is suspected or cardiac surgery is anticipated. If there is coronary artery disease, both CABG and mitral valve replacement can be done in the same sitting.

Treatment

Medical Therapy

- Mild mitral stenosis in sinus rhythm does not require any treatment.
- If the patient develops atrial fibrillation, it should be treated with oral digoxin, a β blocker, or a calcium channel blocker to control heart rate.
- Anticoagulation with warfarin should be done (target INR of 2.5 to 3.5) to prevent clot formation if there is atrial fibrillation.
- Although infective endocarditis in pure mitral stenosis is rare, antibiotic prophylaxis is advised before any invasive procedures.
- Early symptoms of mitral stenosis such as mild dyspnea and orthopnea can usually be treated with diuretics. When symptoms worsen to more than mild or if pulmonary hypertension develops, mechanical correction of the stenosis is necessary.

Mechanical Correction of the Stenosis

- This is done by mitral valvotomy. Mitral valvotomy can be done by by two techniques: Percutaneous balloon mitral valvotomy and surgical valvotomy.

Balloon Mitral Valvotomy (BMV)

- A catheter is passed into the right atrium via the femoral vein. The inter-atrial septum is then punctured and the catheter is advanced into the left atrium and then across the mitral valve. A balloon is then passed over the catheter into the mitral valve and inflated briefly to split the fused valve commissures. This procedure is performed under local anesthesia in the cardiac catheter laboratory. This procedure may result in mitral regurgitation which may require mitral valve repacement.
- Contraindications to the procedure include more than mild mitral regurgitation, calcified mitral valve (valve cannot be opened), and involvement of subvalvular apparatus. The presence of thrombus in the left atrium is also a contraindication to balloon valvotomy because it can be dislodged leading to systemic emboli. Hence, presence of clot should be ruled out by transesophageal echocardiography prior to this technique. The short- and long-term results of this procedure are similar to surgical valvotomy, with less morbidity and mortality rate. Hence, this has become the procedure of choice for suitable patients.

Surgical Valvotomy

- This procedure is done for patients in whom percutaneous valvotomy is not possible, unsuccessful, or in those with restenosis. Here, the cusps are carefully dissected apart under direct vision. Cardiopulmonary bypass is required for this procedure.

Mitral Valve Replacement

- Replacement of the mitral valve is necessary when:
  - Significant mitral regurgitation is present
  - Mitral valve is badly damaged and calcified, hence cannot be opened without producing significant regurgitation
  - There is thrombus in the left atrium.
- Either mechanical prosthetic valves or bioprosthetic valves can be used to replace the miral valve.
- Mechanical prosthetic valves include caged-ball valve (Starr-Edwards prosthesis) and tilting disc valve (Björk-Shiley valve). Mechanical prosthetic valves require lifelong anticoagulation.
- Bioprosthetic valves include porcine bioprosthetic valve and pericardial xenograft prosthetic valve. Bioprosthetic valves do not last long and hence are not used for patients below 35 years. Bioprosthetic valves do not require anticoagulation and hence are especially useful in pregnancy when oral anticoagulants are contraindicated.

Q. Discuss the etiology, clinical features, investigations and management of mitral regurgitation.

- Mitral regurgitation (MR) is defined as an abnormal reversal of blood flow from the left ventricle (LV) to the left atrium (LA).

Etiology

- Rheumatic heart disease (most common cause).
- Mitral valve prolapsed.
- Ischemic heart disease (due to papillary muscle dysfunction or rupture of chordae tendinea).
- Infective endocarditis—mitral regurgitation may result from destruction of the mitral valve leaflets.
- Myocarditis (due to dilatation of left ventricle).
- Dilated cardiomyopathy (due to dilatation of left ventricle).
- Aortic valve disease (due to dilatation of left ventricle).
- Hypertrophic cardiomyopathy—left ventricular contraction is disorganized and mitral regurgitation often develops.
- Connective tissue disorders—systemic lupus erythematosus (SLE) may cause mitral regurgitation due to Libman-Sacks endocarditis.
- Marfan's syndrome and Ehlers-Danlos syndrome cause mitral regurgitation due to myxomatous degeneration of the valve.
- Trauma (after balloon mitral valvotomy and blunt chest trauma).

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- Congenital (endocardial cushion defects, endocardial fibroelastosis).
- Cardiac surgery.
- Chest trauma.
- Drugs, e.g. fenfluramine.
- Out of these causes, ruptured chordae tendineae, ischemic papillary muscle dysfunction or rupture, infective endocarditis, cardiac surgery and chest trauma cause acute severe mitral regurgitation.

Pathophysiology

- Regurgitation of blood into the left atrium increases the left atrial pressure and leads to left atrial dilatation. In long standing mitral regurgitation, increase in left atrial pressure may not be present due to atrilal dilatation which accomodates the regurgitant blood. However, in acute regurgitation there can be significant increase in left atrial pressure leading to pulmonary venous congestion, pulmonary edema and pulmonary HTN.
- Pulmonary HTN leads to right ventricular hypertrophy and right heart failure.
- Regurgitated blood as well as blood coming from pulmonary veins both enter the left ventricle in diastole leading to volume overload. Volume overload of left ventricle leads to left ventricular hypertrophy, dilatation and failure.

Clinical Features

History

- Mild mitral regurgitation can remain silent for many years.
- Patients may c/o palpitations due to increased stroke volume
- Dyspnea, orthopnea and PND can occur due to pulmonary venous congestion, pulmonary edema and left ventricular failure.
- Fatigue and lethargy develop due to reduced cardiac output as the blood regurgitates back into left atrium during systole.
- Patients c/o peripheral edema in the late stages of the disease due to right heart failure.
- Clot formation in the dilated left atrium leading to systemic emboli can occur,but less common than in mitral stenosis.
- Patients may present with fever due to infective endocarditis.

Physical Examination

- Pulse may be irregularly irregular if there is atrial fibrillation.
- Cardiac apex is displaced laterally and outward due to dilated and hypertrophied left ventricle.
- Palpation may reveal a hyperdynamic, diffuse apex beat and a systolic thrill. Parasternal heave may be present due to right ventricular hypertrophy.
- Auscultation reveals soft S_1 due to incomplete opposition of the mitral valve, pansystolic murmur (PSM) due to regurgitation of blood throughout the systole. PSM is loudest at the apex and may radiate to other areas and axilla. S_3 may be heard due to rapid filling of the left ventricle in diastole by the large volume of blood coming from left atrium. Sometimes a short mid-diastolic flow murmur may follow the third heart sound due to increased flow across the mitral valve. Loud P2 may be present due to pulmonary HTN. Bilateral basal lung crepitations may be present due to pulmonary venous congestion.
- Signs of right heart failure such as raised JVP, and peripheral edema, congestive hepatomegaly may be present.

Investigations

Chest X-ray

- Chest X-ray may show cardiomegaly due to left atrial and left ventricular enlargement. Prominent pulmonary artery and vasculature may be seen due to pulmonary HTN.

Electrocardiogram

- The ECG usually shows LV hypertrophy and left atrial enlargement. Atrial fibrillation may be present.

Echocardiogram

- This is the investigation of choice to confirm and assess the extent of mitral regurgitation. It shows the dilated left atrium and left ventricle. Color flow Doppler can determine the severity of regurgitation. Echo can also show the cause of regurgitation (like chordal or papillary muscle rupture) and also the complications of mitral regurgitation (like left atrial clot formation, infective endocarditis and pulmonary HTN). Transesophageal echocardiography can more exactly assess the anatomy and abnormalities of mitral valve which is useful before surgery.

Cardiac Catheterization

- This is helpful to accurately assess the severity of the lesion and to to assess coronary arteries in patients above 40 years of age.

Complications

- Atrial fibrillation
- Systemic embolism

- Infective endocarditis
- Left ventricular failure
- Pulmonary HTN
- Right ventricular failure

Treatment

Medical Therapy

- Mild mitral regurgitation without any symptoms can be managed conservatively by following the patient with serial echocardiograms.
- Infective endocarditis prophylaxis if indicated.
- ACE inhibitors reduce LV volume and afterload and hence decrease mitral regurgitation.
- Diuretics, beta-blockers and dogoxin are helpful to treat heart failure.
- When atrial fibrillation develops, long-term anti-coagulation is required to prevent clot formation.

Surgical Therapy

- Mitral valve repair or replacement is indicated if there is evidence of progressive cardiac enlargement. Most patients with the symptoms of dyspnea, orthopnea, or fatigue should undergo surgery.
- Acute mitral regurgitation, as seen with chordal or papillary muscle rupture or infective endocarditis, requires emergency mitral valve replacement.
- Percutaneous mitral valve repair can be tried in selected patients.

Q. Mitral valve prolapse (MVP).

- MVP is also known as systolic click-murmur syndrome, Barlow's syndrome, floppy-valve syndrome, and billowing mitral leaflet syndrome. Here mitral valve leaflets prolapse into the left atrium during systole.

Etiology

Table 3.28 Etiology of MVP

• Excessively large mitral valve leaflets • Enlarged mitral annulus • Abnormally long chordae • Papillary muscle dysfunction • Myxomatous degeneration of the mitral valve leaflets • Connective tissue diseases: Marfan's syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta	• Rheumatic heart disease • Ischemic heart disease • Cardiomyopathies • Thyrotoxicosis • Idiopathic

Pathophysiology

- During ventricular systole, a mitral valve leaflet (most commonly the posterior leaflet) prolapses into the left atrium. This may result in abnormal ventricular contraction, papillary muscle strain and some mitral regurgitation. Usually the syndrome is not hemodynamically serious. Thromboembolism can occur rarely.

Clinical Features

History

- Most patients with MVP are asymptomatic.
- Some patients complain of chest pain, palpitation, light-headedness and syncope.
- Chest pain is the most common symptom and is usually felt in substernal area with stabbing quality. Exact cause of chest pain is not known but may be due to papillary muscle ischemia because of excessive tension on the papillary muscles during systole.
- Palpitation and syncope may be due to autonomic dysfunction which is common in MVP.
- Transient ischemic attacks may occur due to platelet aggregation and emboli formation.
- Sudden cardiac death due to fatal ventricular arrhythmias is a very rare but recognized complication.

Physical Examination

- The most common sign is a mid or late systolic click, which occurs due to sudden prolapse of the valve and the tensing of the chordae tendinea during systole. This click may be followed by a late systolic murmur owing to some regurgitation. With more regurgitation, the murmur becomes pansystolic. Maneuvers that make the left ventricle smaller, such as the Valsalva maneuver, or standing position due to decreased venous return, make the click and murmur more prominent. This happens because of increased prolapse of mitral valve leaflets into the left atrium when the ventricular volume is less. Conversely, squatting and isometric exercise, which increase LV volume, diminish the click and murmur.

Investigations

ECG

- It is usually normal but sometimes nonspecific ST-T changes in leads II, III and aVF may be seen.

Echocardiogram

- This is the investigation of choice to confirm MVP. Two-dimensional echo-cardiography shows posterior movement of one or both mitral valve cusps into the left atrium during systole. Echo can also show if there is any associated mitral regurgitation.

Treatment

- Most patients with MVP have a benign clinical course. No treatment is required for asymptomatic patients
- However some may progress to have mitral regurgitation and infective endocarditis. Patients with significant mitral regurgitation require standard infective endocarditis prophylaxis before invasive procedures.
- Palpitations and chest pain can be controlled by beta-blockers like propranolol.
- Antiplatelet agents such as aspirin should be given to patients with transient ischemic attacks.

Q. Classify aortic stenosis (AS). Describe the etiology, clinical features, investigations, and management of valvular aortic stenosis.

Q. Clinical assessment of severity of aortic stenosis.

- Aortic stenosis is the obstruction of blood flow across the aortic valve.
- The normal aortic valve area is 3 to 4 cm^2. When the area is less than this, it is called aortic stenosis. In severe aortic stenosis, valve area is less than 1 cm^2.
- AS can be valvular, subvalvular or supravalvular.

Etiology

Table 3.29 Etiology of aortic stenosis

Valvular	Subvalvular
• Congenital bicuspid valve with superimposed calcification • Age-related degenerative calcific AS (aortic sclerosis) • Rheumatic heart disease	• Membranous diaphragm • Tunnel deformity • Hypertrophic obstructive cardiomyopathy
Supravalvular • Williams' syndrome • Familial hypercholesterolemia • Hourglass constrction of aorta • Hypoplasia of aorta	

- ***Congenital aortic valve stenosis*:** Congenitally abnormal (usually bicuspid) aortic valve can undergo progressive narrowing due to turbulent blood flow. Such congenitally abnormal aortic valves are common in men.
- ***Rheumatic fever*:** Rheumatic endocarditis produces commissural fusion, thickening and calcification of aortic valve leading to narrowing. Rheumatic AS is almost always associated with involvement of the mitral valve and by associated severe AR.
- ***Age-related degenerative calcific AS (also known as senile AS or aortic sclerosis)*:** About 30% of persons >65 years exhibit aortic valve sclerosis. An ejection systolic murmur may be heard but true stenosis is rare. Valve changes are due to inflammatory reaction similar to atherosclerosis.
- ***Hypertrophic cardiomyopathy*:** This condition is associated with massive hypertrophy of the inter-ventricular septum which blocks the ventricular outflow during systole. It causes subaortic obstruction.

Pathophysiology

- Obstruction to left ventricular outflow leads to increased left ventricular pressure and compensatory concentric hypertrophy. The hypertrophied LV muscle mass elevates myocardial oxygen requirements. In addition, coronary vessels may be compressed by increased intraventricular pressure leading to dereased blood flow. Both these factors lead to ischemia of myocardium which increases on exertion.
- Since there is obstruction to LV outflow, cardiac output cannot increase on exertion, which leads to exertional syncope, chest pain and dyspnea. Syncope and light-headedness is due to decreased cerebral perfusion.
- BP may also drop during exertion due to peripheral vasodilation.
- Ultimately, left ventricle may dilate and fail.

Clinical Features

History

- Patient is usually asymptomatic until aortic stenosis is moderately severe (aortic orifice is one-third of its normal size).
- When the AS is moderate to severe, exercise-induced syncope, angina and dyspnea develop. Orthopnea and PND may be present if there is heart failure. When these symptoms develop, prognosis is poor and death usually occurs within 2 to 3 years unless surgical intervention is done.

Physical Examination

- Pulse is of low volume and slow-rising or plateau in nature.
- The apex beat is usually not displaced unless there is LV failure and dilatation. Apex is diffuse and well sustained.
- A systolic thrill may be felt in the aortic area due to turbulent blood flow through narrowed aortic valve.
- Auscultation shows a classic ejection systolic murmur which is usually 'diamond shaped' (crescendo-decrescendo). More severe the AS, the longer the murmur because longer ejection time is needed. The murmur is rough in quality, best heard in the aortic area with patient leaning forward and breath held in expiration. It radiates

to carotid arteries especially to the left carotid. The murmur peaks in the mid or late systole because the flow is maximum during the middle of systole. The intensity of the murmur and the severity of AS do not have any correlation because in severe cases, the murmur may be inaudible due to reduced flow. Sometimes the murmur may not be heard in aortic area and heard only over the LV apex, mimicking mitral regurgitation (Gallvardin's phenomenon).

- A systolic ejection click may be heard before the mumur. Presence of an ejection click suggests that the LV outflow obstruction is due to aortic valve involvement and not due to supravalvular or subvalvular causes.
- Aortic component of second heart sound (A_2) is delayed, resulting in narrow splitting of second heart sound in mild to moderate AS. Reversed splitting of the second heart sound may be seen in severe AS.
- When the aortic valve becomes immobile due to severe stenosis or calcification, aortic second heart sound becomes soft or inaudible.
- Left ventricular S_3 may be heard in left heart failure. An S_4 gallop is common due to stiff left ventricle.

Clinical Assessment of Severity of Aortic Stenosis

- Severe aortic stenosis is suggested by one or more of the following findings:
  - Low systolic BP
  - Heaving apex
  - Soft A_2 or single second heart sound
  - Paradoxical splitting of S_2
  - Harsh, loud, long ESM with late peaking
  - Orthopnea, PND and S_3

Investigations

Chest X-ray

- In the initial stages of AS, chest X-ray shows a normal sized heart. But in later stages, when there is dilatation of heart due to failure, there is cardiomegaly. Ascending aorta shows dilatation because turbulent blood flow above the stenosed aortic valve produces so-called 'post-stenotic dilatation'. Sometimes aortic valve calcification may be visible on X-ray.

ECG

- The ECG shows left ventricular hypertrophy. In advanced cases, left ventricular 'strain' pattern due to 'pressure overload' (depressed ST segments and T wave inversion in leads orientated towards the left ventricle (i.e. leads I, AVL, V5 and V6) is seen.

Echocardiogram

- Echo shows LV hypertrophy and thickened, calcified, immobile aortic valve cusps. Transesophageal echo shows the obstructed aortic orifice very well. Echo can also show other valvular abnormalities such as MS and AR, which may accompany AS, and to identify non-valvular causes of LV outflow obstruction such as obstructive hypertrophic cardiomyopathy.

Cardiac Catheterization

- Catheterization of the left side of the heart and coronary angiography should be done in patients with severe AS who are being considered for surgery. Aortic valve replacement and CABG can be carried out at the same time if there is coronary artery disease.

Natural Course of AS

- AS is a progressive disease, with 0.1 cm²/year reduction in the valve area. Symptomatic patients usually die within 4 years after the onset of symptoms.
- Death usually occurs due to congestive heart failure or arrhythmias.

Treatment

Medical Treatment

- Patients with severe AS should avoid strenuous physical activity.
- Nitrates can be used for angina.
- Sodium restriction, diuretics and digoxin can be used to treat congestive heart failure.
- HMG-CoA reductase inhibitors (statins) have been shown to slow the progression of leaflet calcification and aortic valve area reduction. Hence, treatment with these agents should be considered for all patients.
- Infective endocarditis prophylaxis.

Balloon Aortic Valvotomy

- This procedure can be used in children and young adults with congenital, noncalcific AS. It is not recommended for adults because of high restenosis rate, except as a "bridge to operation" in patients with severe LV dysfunction who are too ill to tolerate surgery.

Surgical Treatment

- Patients with severe calcific AS (valve area <1.0 cm²) who are symptomatic, those with LV dysfunction, and those with an expanding poststenotic aortic dilatation require aortic valve replacement. Asymptomatic patients should be followed up regularly for development of symptoms and echocardiography should be done to assess the progression of AS.

Q. Aortic sclerosis (age-related degenerative calcific aortic sclerosis or senile aortic sclerosis).

- Aortic sclerosis refers to aortic valve thickening (sclerosis) which can progress to aortic stenosis.
- It is common in elderely.
- Pathologically it is characterized by lipid accumulation and calcification of the valve.
- It is usually asymptomatic. Physical examination may show an ejection systolic murmur, best heard over the aortic area. In general, the murmur is brief and not very loud. Carotid pulse and S_2 are normal indicating the absence of aortic stenosis.
- Echocardiography shows leaflet thickening, stiffness, and/or increased echogenicity (calcification) of the aortic valve. Leaflet excursion is normal as the commissures are not fused.
- *Clinical significance*: Aortic sclerosis can progress to aortic stenosis. It is a marker for increased cardiovascular risk probably due to increased rate of atherosclerosis.
- ***Management***: HMG Co-A reductase inhibitors and ACE inhibitors may slow the progression of calcification and prevent future aortic stenosis. There is no need for endocarditis prophylaxis.

Q. Discuss the etiology, clinical features, investigations and management of aortic regurgitation (AR).

Q. Peripheral signs of aortic regurgitation (AR).

- Aortic regurgitation can be either due to problem in the valve itself or problems in the aortic root. It can be acute or chronic. Rheumatic fever and infective endocarditis are the commonest causes of AR.

Etiology of AR

Table 3.30 Etiology of AR

Aortic valve problems	Aortic root problems
• Bicuspid aortic valve • Infective endocarditis • Rheumatic heart disease • Anorexigenic drugs (fenfluramine) • Ruptured sinus of valsalva aneurysm • Failure of prosthetic heart valve • Trauma • Aneurysm of aorta • Takayasu's disease	• Marfan's syndrome • Severe hypertension • Aortic dissection • Syphilis • Ankylosing spondylitis • Psoriatic arthritis • Idiopathic dilatation of the aorta • Osteogenesis imperfecta

- Out of these, acute aortic regurgitation is caused by acute rheumatic fever, infective endocarditis, aortic dissection, ruptured sinus of Valsalva, and failure of prosthetic heart valve.

Pathophysiology

- In AR, some of the blood pumped into the aorta by the left ventricle comes back into the left ventricle through the aortic valve during diastole. This is also joined by the blood coming from left atrium which leads to volume overload of left ventricle (increase in end diastolic volume). There is increase in stroke volume of left ventricle due to this volume overload.
- Increase in stroke volume causes all the peripheral signs of aortic regurgitation. Chronic volume overload causes eccentric hypertrophy and dilatation of left ventricle, which may ultimately fail.
- Increased stroke volume leads to increase in systolic BP and high volume pulses. Since the blood ejected into the aorta regurgitates back into left ventricle, there is drop in diastolic BP. Rise in systolic BP and fall in diastolic BP leads to increased pulse pressure
- An early diatolic murmur is produced due to blood regurgitating back into left ventricle.
- In advanced cases of AR, there may be increase in left atrial and pulmonary venous pressures leading to right heart failure.
- Myocardial ischemia may occur in patients with AR because myocardial oxygen requirement is elevated by both LV hypertrophy and systolic HTN.
- Acute AR may lead to left ventricular failure because left ventricle is not prepared to handle this sudden volume overload.

Clinical Features

Symptoms

- In early stages, patients may remain asymptomatic.
- Patients may c/o palpitations and head pounding due to increased stroke volume.
- When left ventricular dysfunction appears, symptoms such as exertional dyspnea, orthopnea, PND and fatigue appear. Thickened left ventricular wall also leads to diastolic dysfunction which can also cause above symptoms even if systolic function is normal.
- Anginal chest pain may occur in patients with severe AR due to increased myocardial oxygen demand but less common than in aortic stenosis.

Signs

- Aortic regurgitation produces a myriad of signs due to increased stroke volume and hyperdynamic circulation.

- The pulse is bounding or collapsing. Systolic BP is typically high and diastolic BP low leading to wide pulse pressure. Systolic pressure in the upper limb is at least 40 mm Hg or more than the lower limb (Hill's sign).
- The following peripheral signs may be present in aortic regurgitation.
- All the above peripheral signs may be absent in acute aortic regurgitation.

Table 3.31 Peripheral signs of aortic regurgitation

Sign	Description
• Corrigan's neck sign or dancing carotids	Prominent carotid pulsations in the neck
• Quincke's sign	Systolic plethora and diastolic blanching in the nail bed when gentle pressure is applied on the nail
• De Musset's sign	Head nodding with each heartbeat
• Duroziez's sign	Combined systolic and diastolic bruits created by compression of the femoral artery with the stethoscope. It is seen in severe AR
• Traube's sign (pistol shot femorals)	A sharp bang heard on auscultation over the femoral arteries in time with each heartbeat
• Hill's sign	Systolic pressure in the upper limb is at least 40 mm Hg or more than the lower limb.
• Collapsing pulse (water-hammer pulse; Corrigan's pulse)	This is characterized by rapid upstroke, rapid down stroke and high volume
• Pulsus bisferiens	This is a pulse with double peak. It is seen in severe AR
• Müller's sign	Pulsations of the uvula
• Lighthouse sign	Alternate flushing and blanching of the forehead
• Becker's sign	Visible pulsations of retinal artery and pupil
• Rosenbach's sign	Systolic pulsations of the liver
• Gerhardt's sign	Systolic pulsations of the spleen
• Mayne's sign	More than a 15 mm Hg decrease in diastolic blood pressure with arm elevation from the value obtained with the arm in the standard position

- All these peripheral signs are not specific for AR, since they can be seen in any condition associated with a marked increase in stroke volume and a hyperdynamic circulation. Examples are sympathetic hyperactivity, anemia, fever, pregnancy, thyrotoxicosis, large arteriovenous fistula, patent ductus arteriosus, and severe bradycardia.
- The apex beat is displaced laterally and downwards and is forceful in quality.
- On auscultation, S_1 and S_2 are usually normal. S_2 is followed by an early diastolic high pitch blowing murmur heard best along the left sternal border with the patient sitting and leaning forward.
- The regurgitant jet can impinge on the anterior mitral valve leaflet making it vibrate and cause a middiastolic murmur (Austin Flint murmur). Austin Flint murmur can be mistaken for middiastolic murmur of mitral stenosis. However, MS murmur is usually accompanied by a thrill, which is, absent in Austin flint murmur.
- Because of increased stroke volume, there can be a functional ejection systolic murmur mimicking aortic stenosis. However, absence of slow rising pulse differentiates functional ejection systolic murmur from true AS.

Clinical Assessment of Severity of AR

- Presence of one or more of the following features suggests that AR is severe:
  - Peripheral signs
  - Pulsus bisferiens
  - Hill's sign more than 60 mm Hg
  - Hyperdynamic apex
  - Early diastolic murmur lasting more than two-thirds of diastole
  - Presence of Austin Flint murmur

Investigations

Chest X-ray

- Chest X-ray shows cardiomegaly due to left ventricular enlargement. Post-stenotic dilatation of the aorta may be visible. Aortic valve calcification may be visible in some cases.

ECG

- The ECG features of left ventricular hypertrophy with strain pattern (tall R waves in the left-sided chest leads, deep S waves in the right-sided leads, ST-segment depression and T-wave inversion in leads I, aVL, V_5, and V_6).

Echocardiogram

- Echo can confirm the diagnosis and cause of AR. It can also assess LV function and the status of other valves. The regurgitant jet causing fluttering of anterior mitral leaflet can be detected by color flow Doppler.

Cardiac catheterization

- It is the most accurate way of confirming and assessing the degree of AR. It can also assess LV function and status of coronary arteries.

Other Tests

- VDRL and TPHA to rule out syphilitic etiology.
- ANA, RA factor, CRP and ESR to rule out connective tissue disease.
- ASO titre and throat swab culture if rheumatic etiology is suspected.

Treatment

Medical

- For asymptomatic patients with normal LV function, afterload reduction is recommended because it delays or reduces the need for aortic valve surgery. Vasodilarors like ACE inhibitors, nitrates, hydralazine and nifedifine are helpful to reduce afterload.
- Digoxin, diuretics, ACE inhibitors and salt restriction are useful if there is heart failure.
- The underlying cause of aortic regurgitation (e.g. rheumatic, syphilitic or infective endocarditis) requires specific treatment.
- Infective endocarditis prophylaxis is recommended for AR.

Surgical

- Surgical aortic valve replacement is necessary after the onset of LV dysfunction but before the development of severe symptoms.
- In general, operation should be carried out in patients with left ventricular ejection fraction (LVEF) <55% or a LV end-systolic volume >55 ml/m^2. These parameters have been referred to as the "55/55 rule."
- Surgical treatment is also necessary in patients with acute severe AR.

Q. Austin Flint murmur.

- This is a mid-diastolic, low-pitched, rumbling murmur heard over the apex in severe aortic regurgitation.
- It is due to the aortic regurgitant jet impinging on anterior mitral leaflet causing it to vibrate.
- It may be confused with mid-diastolic murmur (MDM) of mitral stenosis. MDM of mitral stenosis is characterized by loud S1, opening snap, and presystolic accentuation. All these features are absent in Austin Flint murmur.

Q. Tricuspid stenosis (TS).

- This is an uncommon valve lesion, seen more often in women than in men.

Etiology

- TS is usually due to rheumatic heart disease and is frequently associated with mitral and/or aortic valve disease. Rarely can it be due to carcinoid syndrome or congenital.

Pathophysiology

- Tricuspid valve stenosis results in collection of blood in the right atrium raising its pressure. Rise in right atrial pressure causes systemic venous congestion resulting in hepatomegaly, peripheral edema and ascites.
- Reduced blood flow into right ventricle results in reduced blood flow into left ventricle and hence reduced cardiac output.
- Cardiac output cannot increase on exertion because TS will not allow increased venous return into right and then left ventricle.

Clinical Features

- Patients usually c/o dyspnea and fatigue due to reduced cardiac output.
- Abdominal pain may be there due to congestive hepatomegaly. JVP is raised and shows a prominent 'a' wave. Ascites and peripheral edema may be present.
- A mid-diastolic murmur may be heard at the lower left sternal border, which becomes louder on inspiration. A tricuspid opening snap may occasionally be heard.
- Patients usually develop atrial fibrillation due to right atrial dilatation.

Investigations

- Chest X-ray shows prominent right atrial bulge.
- ECG shows features of right atrial enlargement such as tall, peaked, P waves (>3 mm) in lead II and prominent, upright P waves in lead V_1.
- Echo may show a thickened and immobile tricuspid valve.

Treatment

- Systemic venous congestion can be brought down by diuretics and salt restriction.
- Surgical repair should be carried out in patients with moderate or severe TS. If repair is not possible tricuspid valve replacement is necessary with preferably a bio-prosthetic valve.

Q. Tricuspid regurgitation.

Etiology

- Tricuspid regurgitation is usually functional secondary to dilatation of the tricuspid annulus. Dilatation of the tricuspid annulus occurs whenever there is right ventricular dilatation, e.g. in cor pulmonale, myocardial infarction and pulmonary hypertension.
- Organic tricuspid regurgitation may occur with rheumatic heart disease, infective endocarditis, carcinoid syndrome, and congenital abnormalities.

Clinical Features

- The symptoms of tricuspid regurgitation are those of right-sided heart failure, including ascites, edema, and right upper quadrant pain due to congested liver. JVP is raised with prominent '*v*' wave.
- Regurgitation into the hepatic veins causes hepatic enlargement and liver pulsation.
- Right ventricular enlargement produces a parasternal heave in the left sternal border.
- A blowing pansystolic murmur is heard at the lower left sternal edge, which increases on inspiration.
- Atrial fibrillation is common due to right atrial enlargement.

Investigations

- Chest X-ray shows right atrial and ventricular enlargement.
- ECG shows features of right ventricular hypertrophy.
- ECHO can confirm the presence and severity of TR and show right atrial and ventricular enlargement.

Treatment

- Functional tricuspid regurgitation usually disappears with treatment of underlying disease.
- Severe organic tricuspid regurgitation may require operative repair of the tricuspid valve (annuloplasty or plication). If repair is not possible, valve replacement may be necessary.
- In drug addicts with infective endocarditis of the tricuspid valve, surgical removal of the valve is recommended to eradicate the infection.

Q. Pulmonary stenosis (PS).

Etiology

- PS is usually a congenital lesion due to maternal rubella infection during pregnancy. Congenital pulmonary stenosis may be isolated or associated with Fallot's tetralogy.
- Other causes are rheumatic fever and carcinoid syndrome.
- Pulmonary stenosis may be valvular, subvalvular or supravalvular.

Clinical Features

- PS causes obstruction to right ventricular emptying and results in right ventricular hypertrophy, right heart failure and right atrial enlargement. Patients may have signs and symptoms of right heart failure. JVP is raised with prominent 'a' wave.
- PS decreases the blood flow from right to left ventricle and hence causes decreased cardiac output which does not increase on exertion. This causes fatigue and syncope on exertion.
- A midsystolic ejection murmur is heard in the pulmonary area which increases on inspiration. The murmur is often associated with a thrill. P2 is usually delayed and soft.

Investigations

- Chest X-ray shows a prominent pulmonary artery due to poststenotic dilatation.
- ECG shows features of right atrial and right ventricular hypertrophy.
- Echo can confirm the diagnosis and assess the severity of PS.
- Cardiac catheterization can also assess the level and degree of the stenosis by measuring the systolic pressure gradient across pulmonary valve.

Treatment

- Mild to moderate PS does not require endocarditis prophylaxis.
- Treatment of severe pulmonary stenosis requires balloon valvotomy or surgery.

Q. Pulmonary regurgitation (PR).

- PR is usually due to dilatation of the pulmonary valve ring, which occurs with pulmonary hypertension.
- It is characterized by an early diastolic murmur, which is difficult to distinguish from the murmur of aortic regurgitation. This murmur is called Graham Steell murmur.
- Pulmonary regurgitation usually causes no symptoms and treatment is rarely necessary.

Q. Discuss the causes and differential diagnosis of ejection systolic murmur (ESM).

- Ejection systolic murmurs (ESM) are due to turbulent forward flow across the aortic or pulmonary valve. Turbulence is produced by obstruction to blood flow, vascular dilation, and increase in the velocity of flow or a combination.
- The ejection of blood begins after closure of the atrioventricular (mitral and tricuspid) valves and is preceded by the time it takes for the ventricular pressures to sufficiently exceed the aortic and pulmonary diastolic pressure and force open the aortic and pulmonary valves. Because of this delay, there is a silent interval between the first heart sound (S_1 is produced by closure of the AV valves) and onset of the murmur.

- An ESM begins after S_1, terminates before A_2, clearly heard over the cardiac apex, and is usually crescendo-decrescendo configuration.

Causes

Table 3.32 Causes of ejection systolic murmurs

Valvular diseases	Miscellaneous
• Aortic stenosis • Pulmonary stenosis • Hypertrophic cardiomyopathy • Aortic sclerosis • Bicuspid aortic valve • Tetralogy of Fallot **Flow murmurs (functional murmurs)** • Hyperdynamic states (thyrotoxicosis, anemia, AV fistula) • Pregnancy • Increased systolic flow across the valve (ASD, aortic regurgitation, mitral regurgitation)	• Coarctation of aorta • Straight back syndrome • Aneurysm of ascending aorta

Differential Diagnosis

Aortic Valve Sclerosis

- The murmur is brief and not very loud. It is usually best heard over the right second interspace.
- It is not associated with hemodynamic consequences. Carotid pulse and S_2 are normal.

Aortic Stenosis

- Murmur is harsh and best heard in the right second intercostal space. It radiates to carotids especially to right carotid.
- Aortic ejection click sound may be heard.
- It produces hemodynamic consequences such as slow rising pulse and low systolic BP.
- LVH is present and apex is heaving type.
- Systolic thrill at right second intercostal space may be present.
- S_2 may be normal, narrowly split or paradoxically split with decreased intensity of A_2.

Bicuspid Aortic Valve (Uncomplicated)

- Murmur is short and soft. It is heard over aortic area.
- Normal S_1 and S_2
- Aortic ejection click may be present.
- Short, early aortic diastolic murmur may be present.
- Normal cardiac impulse.

Pulmonary Stenosis

- Murmur is harsh and best heard over the left second interspace. It may radia :o the left side of the neck and is frequently accompanied by a palpable thrill.
- Signs of RVH may be present such as left parasternal heave and prominent epigastric pulsations.
- Pulmonary ejection sound may be heard.
- S_2 is widely split with a decreased intensity of P_2.

Atrial Septal Defect (ASD)

- ESM is produced due to increased flow across pulmonary valve. Murmur is short and soft. It is heard over pulmonary area.
- S_2 is widely split and fixed.
- Mid-diastolic rumble over the tricuspid area.
- Pulsation in the pulmonary area due to dilated pulmonary artery
- Hyperdynamic left parasternal impulse

Idiopathic Dilatation of the Pulmonary Artery

- Murmur is best heard over pulmonary area. It is short and soft.
- Pulsation in the pulmonary area due to dilated pulmonary artery
- S_1 normal; S_2 may be widely split.
- Pulmonary ejection sound.
- Short, early pulmonary diastolic murmur may be present.
- Normal cardiac impulse.

Coarctation of Aorta

- Murmur can extend beyond the second heart sound, at the left paravertebral interscapular area, due to flow across the narrow coarctation area.
- Continuous murmurs may be due to flow through large collateral vessels.
- Cardiac examination is usually normal. S_1 and S_2 are usually normal.
- Underdeveloped lower segment of the body.
- Differential pressures between the upper and lower limbs (hypertension in the upper limbs).
- Radiofemoral delay.
- Heaving apical impulse.

Hypertrophic Cardiomyopathy (HCM)

- Murmur is best heard at the apex and left lower sternal border.
- Murmur increases with maneuvers which increase the obstruction. These are standing, Valsalva maneuver, and nitroglycerin. Murmur decreases on sitting or squatting, with handgrip, and following passive elevation of the legs.

- Rapidly rising (jerky) carotid pulse.
- Double apical impulse.

Q. Discuss the causes and differential diagnosis of pansystolic murmur (PSM).

- Pansystolic murmurs (holosystolic murmurs) are heard throught the systole. They occur when the blood flows from a chamber whose pressure throughout systole is higher than pressure in the chamber receiving the flow.

Causes of Pansystolic Murmur

- Mitral regurgiation
- Tricuspid regurgitation
- Ventricular septal defect

Differential Diagnosis of Pansystolic Murmur

Mitral Regurgitation

Murmur

- Murmur is high pitched
- It is best heard with the diaphragm of the stethoscope with the patient in the left lateral decubitus position.
- It usually radiates to left axilla, and inferior angle of the left scapula.

Associated features

- Apex is shifted out and laterally due to left ventricular enlargement in significant MR. Apex is hyperdynamic in character.
- Systolic thrill at the apex.
- S_1 is soft, S_2 is widely split but mobile.
- There may be an S_3 gallop due to high diastolic flow across the mitral valve.
- Loud P_2, parasternal heave and epigastric pulsations due to pulmonary HTN and RVH.
- There may be findings of right heart failure.

Tricuspid Regurgitation

Murmur

- Murmur is best heard with the diaphragm of the stethoscope over the lower left second and third intercostal spaces and along the left sternal border. It may radiate to the epigastrium.
- Intensity of the murmur varies with respiration. It increases during inspiration (Carvallo's sign) due to increase in regurgitant flow following the inspiratory increase in right ventricular volume.

Associated features

- Prominent '*v*' wave and rapid '*y*' descent in the jugular venous pulse
- Hepatomegaly and systolic hepatic pulsation.
- Right ventricular S_3 gallop and a mid-diastolic flow murmur in severe TR.

Ventricular Septal Defect

Murmur

- Murmur is harsh and is best heard along the left sternal border.

Associated features

- High volume collapsing pulse
- Apex is shifted down and out and is hyperdynamic
- S_2 is normal and pulmonary hypertension is absent.

Q. Discuss the causes and differential diagnosis of early diastolic murmur (EDM).

- EDM is a high frequency and (usually) decrescendo murmur that begins with S_2 and results from aortic or pulmonic valve regurgitation.
- Early diastolic murmurs start at the time of semilunar valve closure and their onset coincides with S_2.

Causes

- Aortic regurgitation
- Pulmonary regurgitation
- Left anterior descending artery stenosis.

Differential Diagnosis of Early Diastolic Murmurs

Aortic Regurgitation

- Murmur is high-pitched decrescendo murmur. It has high-frequency and a "blowing" character.
- It begins with A_2 and usually terminates before S_1.
- It is best heard with the diaphragm of the stethoscope over the aortic area or over the left sternal border, with the patient sitting and leaning forward and the breath held in full expiration.
- Murmur radiates towards cardiac apex.
- Apex is hyperdynamic and shifted out and downwards.
- Wide and collapsing pulse.
- Peripheral signs of aortic regurgitation present.

Pulmonary Regurgitation

- The murmur of pulmonary regurgitation due to pulmonary hypertension (Graham Steell murmur) is high-pitched and "blowing." It is decrescendo type.
- The murmur begins with P_2 and is best heard over the left second and third interspaces.

- It may increase in intensity during inspiration.
- P_2 is loud.

Left Anterior Descending Artery Stenosis

- It is caused by turbulent flow across the coronary artery stenosis and indicates moderately severe stenosis.
- Murmur is not widespread like that of aortic regurgitation and usually is best heard over the left second or third interspace lateral to the sternal border.
- Coronary artery bypass surgery abolishes the murmur.

Q. Discuss the causes and differential diagnosis of mid-diastolic murmur (MDM).

- MDM is a low-frequency murmur in mid diastole that results from disturbed inflow through stenotic mitral or tricuspid valve or high volume inflow through normal mitral or tricuspid valve.

Causes of Mid-diastolic Murmurs

- Mitral stenosis
- Tricuspid stenosis
- Atrial myxoma
- Austin Flint murmur
- Carey Coombs murmur
- Flow murmurs (TR, MR, ASD, VSD, PDA)

Differential Diagnosis

Mitral Stenosis

Murmur
- It has a rumbling character and is best heard with the bell of the stethoscope over the apex with the patient in the left lateral decubitus position.
- It starts with an opening snap. Its duration correlates with the severity of mitral stenosis. The longer the duration of the murmur, the more severe is the mitral stenosis.

Associated features
- Tapping apex
- Diastolic thrill at the apex
- Loud first heart sound
- Features of pulmonary HTN (parasternal heave, loud P_2)
- Presence of atrial fibrillation.

Tricuspid Stenosis

Murmur
- Best heard along the left sternal border.
- Intensity of the murmur increases with inspiration (Carvallo's sign).

Associated features
- Peripheral edema and ascites
- Tricuspid opening snap.
- Wide splitting of S_1 due to delayed closure of the tricuspid valve.
- Presence of atrial fibrillation.
- Prominent 'a' wave and slow y descent in the JVP.
- Presystolic hepatic pulsation.

Atrial Myxoma

- Atrial myxoma may cause obstruction of the atrioventricular valves and a mid-diastolic murmur.

Murmur
- Murmur has presystolic accentuation and crescendo character.
- The character and intensity of the murmur may change with position.

Associated features
- A "tumor plop" sound may be present.
- Atrial fibrillation is usually absent.
- No opening snap.
- Systemic features such as fever, fatigue and weight loss may be present.

Austin Flint Murmur

Murmur
- This is an apical diastolic rumbling murmur seen in aortic regurgitation. It is best heard at the apex.

Associated features
- Amyl nitrate inhalation decreases the murmur due to decrease in afterload.
- No opening snap unlike mitral and tricuspid stenosis.
- Peripheral signs of aortic regurgitation present.
- Hyperdynamic apex which is shifted out and downwards.

Carey Coombs Murmur

Murmur
- This is seen in acute rheumatic fever, due to acute mitral valvulitis.
- Murmur is best heard over the apex.

Associated Features
- There may be features of rheumatic fever such as joint pains, erythema marginatum, subcutaneous nodules, etc.

Flow Murmurs

- Mid-diastolic murmurs may occur due to increased flow across the atrioventricular valve even when there is no stenosis. Examples are mitral regurgitation, ASD, VSD, and PDA.

Mitral Regurgitation

- Middiastolic rumbling murmur is best heard over the apex.
- Hyperdynamic apex, which is shifted down and out.
- Left ventricular S_3.
- Systolic thrill at the apex
- Soft S_1
- Pansystolic murmur best heard over the apex and radiating to axilla.

VSD

- Mid-diastolic rumbling murmur is best heard over the apex.
- Hyperdynamic apex which is shifted down and out.
- Left ventricular S_3.
- Systolic thrill at the 3rd or 4th left intercostal space.
- Widely split but mobile S_2.
- Pansystolic murmur best heard over the 3rd or 4th left intercostal space radiating all over the precordium.

Patent Ductus Arteriosus (PDA)

- Middiastolic rumbling murmur is best heard over the apex.
- Hyperdynamic apex which is shifted down and out.
- Left ventricular S_3.
- Continous thrill at the left sternal angle.
- Continous machinery murmur with late systolic accentuation at the left steral border.

Tricuspid Regurgitation (see Differential Diagnosis of Pansystolic Murmurs).

ASD

- Murmur is best heard over the lower left sternal border.
- Visible pulmonary artery pulsations in the left second intercostal space.
- Wide, fixed, splitting of S_2.

Q. Define continuous murmur. Enumerate the causes of continuous murmurs.

- Continuous murmurs are defined as murmurs that begin in systole and extend up to diastole without interruption. Continuous murmurs occur if there is a pressure gradient both in systole and diastole.

Causes

- Patent ductus arteriosus
- Aortopulmonary window
- Rupture of aneurysm of sinus of Valsalva
- Arteriovenous fistulas
- Coarctation of aorta
- Venous hum
- Mammary souffle

Q. Define arrhythmia. Classify different types of arrhythmias.

- An abnormality of the cardiac rhythm is called a cardiac arrhythmia.
- Arrhythmias may cause sudden death, syncope, heart failure, dizziness, and palpitations or can be asymptomatic. They can be either transient or sustained.
- An arrhythmia with a rate of <60 per min is called brady-arrhythmia.
- An arrhythmia with a rate of >100 per min is called tachy-arrhythmia.
- Tachyarrhythmias are more symptomatic than brady-arrhythmias. Tachyarrhythmias can be further divided as supraventricular (arise from the atrium or the atrio-ventricular junction) and ventricular (arise from the ventricles).

Table 3.33 Classification of arrhythmias

Disorders of impulse formation	Disorders of impulse conduction
• **Sinus rhythm** – Sinus arrhythmia – Sinus tachycardia – Sinus bradycardia – Sinus arrest	• **SA nodal block** • **A-V nodal block** – First degree – Second degree (Wenckebach)
• **Atrial rhythm** – Atrial ectopic – Atrial tachycardia – Atrial flutter – Atrial fibrillation – Paroxysmal supraventricular tachycardia	– Third degree (complete heart block) • **Intraventricular blocks** – Right bundle branch block (RBBB) – Left bundle branch block (LBBB)
• **A-V junctional (nodal) rhythm** – A-V junctional escape rhythm – A-V junctional ectopic – A-V junctional tachycardia	– Fascicular blocks; left anterior, left posterior and bifascicular (trifascicular block leads to complete heart block)
• **Ventricular rhythm** – Ventricular escape rhythm (idioventricular rhythm) – Ventricular ectopic – Ventricular tachycardia – Ventricular flutter – Ventricular fibrillation	

Q. Sinus arrhythmia.

Q. Sinus tachycardia.

Q. Sinus bradycardia.

Q. Sick sinus syndrome.

Sinus Arrhythmia

- Fluctuation of autonomic tone due to respiration results in phasic changes of the sinus discharge rate. During inspiration, para-sympathetic tone falls and the heart rate increases, whereas on expiration the heart rate falls. This is known as sinus arrhythmia.
- Sinus arrhythmia is a normal phenomenon and results in a regularly irregular pulse (note: Irregularly irregular pulse is seen in atrial fibrillation). It is more prominent in children and young adults.
- Loss of sinus arrhythmia is seen in autonomic neuropathies (e.g. due to diabetes) and also in transplanted heart.

Sinus Bradycardia

- A heart rate of less than 60 beats per minute originating in sinus node is called sinus bradycardia. It is usually asymptomatic unless the rate is very slow.

Table 3.34 Causes of sinus bradycardia

Physiological	Pathological
• Sleep (due to decreased sympathetic tone) • Elderly • Athletes (due to increased vagal tone)	• Hypothyroidism • Cholestatic jaundice • Raised intracranial pressure • Myocardial infarction (due to ischemia or infarction of sinus node) • Hypothermia • Typhoid fever • Brucellosis • Vasovagal syncope • Severe hypoxia, hypercapnia, acidosis • Acute hypertension • Idiopathic • Drugs (beta blockers)

- Treatment of symptomatic bradycardia includes insertion of temporary pacemaker if there is a reversible cause or permanent pacemaker if the cause is irreversible. Injection of atropine may help temporarily.

Sinus Tachycardia

- A heart rate of more than 100 beats per minute originating in sinus node is called sinus tachycardia. In the ECG, it is characterized by normal P waves, PR interval and QRS complexes. QRS complexes may be broad if there is intraventricular conduction defect. Sinus tachycardia may be experienced as palpitations.

Table 3.35 Causes of sinus tachycardia

Physiological	Pathological
• Anxiety, fear • Exertion	• Fever • Anemia • Hypovolemia • Hypotension • Heart failure • Hyperthyroidism • Phaeochromocytoma • Sympathomimetic drugs (ephedrine, pseudoephedrine, β-adrenoceptor agonists)

- Management includes treating the underlying cause or beta blockers.

Sick Sinus Syndrome

- This refers to episodes of sinus bradycardia, sinoatrial block, or sinus arrest.
- It is caused by idiopathic fibrosis of the sinus node. Other causes are ischaemic heart disease, cardiomyopathy, myocarditis and drugs.
- Patient experiences a combination of symptoms (dizziness, confusion, fatigue, and syncope). These symptoms are due to cerebral hypoperfusion and reduced cardiac output.
- Usually these episodes are intermittent. If the symptoms are recurrent, permanent pace maker insertion is required.

Q. Define ectopic beats (extrasystoles; premature beats). What are the types of ectopic beats?

Q. Supraventricular ectopics (atrial ectopics; atrial premature beats).

Q. Ventricular premature beats (ventricular ectopics, ventricular premature complexes, and VPCs).

- A heart beat occurring as a result of an impulse arising in an area other than SA node is called ectopic beat.
- *Types*: Ectopic beats can be classified based on the area from which they arise: Supraventricular (atrial, junctional) and ventricular.

Atrial Ectopics

- An atrial premature beat (APB), also known as an atrial premature complex (APC), is a premature activation of the atria arising from a site other than the sinus node.

Etiology

- Idiopathic
- Mitral valve prolapse (MVP)
- IHD
- Valvular heart disease (mitral stenosis)
- Hypertrophic cardiomyopathy
- Smoking, alcohol and excess coffee

Clinical Features

- Atrial ectopics may be asymptomatic or cause symptoms such as a sensation of "skipping" or palpitations.
- Atrial ectopics are usually benign but rarely may cause atrial fibrillation and ventricular arrhythmias.

ECG

- Atrial ectopic appears as a P wave that occurs relatively early before the next expected sinus P wave, which has a different morphology from the sinus P wave.
- PR interval may be shorter or longer depending on the site of origin of the atrial ectopic.

Treatment

- Treat the underlying cause
- Asymptomatic patients do not require any treatment
- Symptomatic patients with frequent atrial ectopics may bebefit from beta blockers.

Junctional Ectopics

- These arise within the AV junction. They may conduct both anterograde to the ventricles and retrograde to the atrium, or may demonstrate anterograde and/or retrograde conduction block.

Causes

- Idiopathic
- Hypokalemia
- Digitalis toxicity
- Chronic lung disease
- Acute myocardial infarction

Clinical Features

- They can be asymptomatic or lead to symptoms such as palpitations and missed beats.

ECG

- Junctional ectopics appear as premature beat with a normal QRS complex.
- PR interval of the junctional ectopic is short. P wave is inverted in ECG leads II, II, aVF due to retrograde activation of atria. Sometimes P wave may not appear on ECG due to burial of the wave within the QRS complex or lack of retrograde atrial activation.

Treatment

- Treat the underlying cause.
- Asymptomatic patients do not require nay treatment.
- Symptomatic patients may bebefit from beta blockers and calcium channel blockers.

Ventricular Ectopics

- Also known as ventricular premature complexes (VPC), or ventricular premature beat. These arise from the ventricle and are one of the most common arrhythmias seen.
- Two consecutive PVCs are termed a *couplet*.
- Three or more consecutive PVCs at a rate of 100 beats per minute or more are termed *ventricular tachycardia* (VT).
- Single PVCs may occur sporadically or as bigeminy (every other beat is a PVC), trigeminy (every third beat is a PVC), or higher order periodicities.
- In normal persons, PVCs are not associated with any increase in mortality and morbidty. However, in patients with MI, if frequent (>10 per hour) or complex VPCs (couplets) occur, they are associated with increased mortality.

Etiology

Table 3.36 Etiology of ventricular ectopics

• Idiopathic • Myocardial infarction • Drug toxicity (e.g. digitalis intoxication) • Electrolyte disturbances (e.g. hypokalemia)	• Coronary artery disease • Heart failure • Hypertension • Valvular heart disease (MVP)

Clinical Features

- Can be asymptomatic
- Patient may complain of extra beats, missed beats or heavy beats because it may be the premature beat, the post-ectopic pause or the next forceful sinus beat that is noticed by the patient.
- The pulse is irregular due to premature beats. When a premature beat occurs regularly after every normal beat, 'pulsus bigeminus' occurs.

3

ECG

- Ventricular ectopics have a broad (>0.12 s) and bizarre QRS complex, not preceded by P waves because the impulse arises from an abnormal (ectopic) site in the ventricule and travels through abnormal path (does not travel through normal conducting pathway such as Purkinje fibers).
- Following a premature beat there is usually a complete compensatory pause because the AV node or ventricle is refractory to the next sinus impulse.
- If the VPC comes early ('R on-T' ventricular premature beat occurring simultaneously with the upstroke or peak of the T wave of the previous beat), it may induce ventricular fibrillation in patients with heart disease, particularly in patients following myocardial infarction.

Treatment

- No treatment required for asymptomatic patients.
- Symptomatic patients are treated with beta-blockers or amiodarone.
- Underlying cause should be treated.

Q. Describe the etiology, clinical features, investigations, and management of atrial fibrillation (AF).

- Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of mechanical atrial function.
- AF is the most common arrhythmia in adults. It can be paroxysmal, persistent or chronic. Paroxysmal AF refers to eisodes that terminate spontaneously. Persistent AF refers to episode sustained for more than seven days, or AF that terminates only with cardioversion. Chronic or continuous AF is the one that is unresponsive to cardioversion.

Etiology

Table 3.37 Etiology of AF

• Emotional stress or following surgery, exercise, excessive caffeine use, smoking, and acute alcoholic intoxication	• Rheumatic heart disease (mitral valve disease such as mitral stenosis or mitral regurgitation) • Hypertension • Heart failure • Hyperthyroidism • After coronary artery bypass surgery • COPD • Cardiomyopathy • Pericardial disease • Pulmonary embolism • Idiopathic (lone atrial fibrillation)

Pathophysiology

- During AF, the atria have disorganized, rapid, irregular electrical activity (300–600 per minute). The ventricular response is also irregular and variable (irregularly irregular).
- There is no coordinated mechanical contraction of atria giving rise to turbulence and stasis of blood in the atria leading to clot formation. With subsequent resumption of atrial contraction, clot can go into left ventricle and then into systemic circulation causing embolism.
- Excessive ventricular rate does not allow proper filling of ventricles, which leads to reduced cardiac output, pulmonary congestion, or angina pectoris.

Clinical Features

Symptoms

- Atrial fibrillation can be asymptomatic and detected incidentally in some patients.
- Patients may complain of anxiety, palpitaions, fatigue and dyspnea. Patients may also present with stroke due to systemic embolism.

Signs

- Irregularly irregular pulse which is usally 100–150
- Varying volume of pulse
- Apex pulse deficit
- Loss of 'a' wave in JVP due to absent atrial contraction
- Variable intensity S1
- Signs of cardiac failure such as bilateral basal lung crepitations may be there due to fast heart rate.
- There may be features of underlying disease causing atrial fibrillation.

Complications

- Syncope
- Thromboembolism
- Cardiac failure
- Angina
- Hypotension
- Pulmonary edema

Investigations

- ECG shows varying RR intervals. P waves are absent and there may be undulating baseline instead of P waves.
- Echocardioagram can detect underlying condition such as mitral steonsis and atrial dilatation and clot formation.
- Other tests include complete blood count (to identify anemia), thyroid function tests (to identify hyperthyroidism), serum electrolytes (to identify electrolyte imbalance) and chest X-ray (to identify pneumonia, COPD).

Management

- Goals of treatment:
  - Control of ventricular rate
  - Restoration of sinus rhythm if feasible
  - Prevention of embolic complications
  - Correction of underlying cause.
- If hemodynamically unstable (as evidenced by hypotension, hypoxia, pulmonary edema, angina), electrical cardioversion (DC shock with 100 to 200 joules) is the treatment of choice. If sinus rhythm is not restored, an additional attempt with 360 J is tried. If this also fails, cardioversion may be successful after loading with intravenous ibutilide or intravenous procainamide.
- If hemodynamically stable, further treatment depends on whether the AF onset is of less than 48 hours or more than 48 hours. If onset of AF is less than 48 hours, then cardioversion can be attempted because the risk of a clot developing in thr atria within 48 hours of AF is nil.
- On the other hand, if AF onset is more than 48 hours back, cardiovesrion is risky, because clot formation can occur in the atria, which can be dislodged by cardioversion. For these patients, slowing of ventricular rate should be the initial goal. Ventricular rate control is achieved by intravenous β-blockers (esmolol, metoprolol) and/or calcium channel blockers (*verapamil* or *diltiazem*). Both prolong the refractory period of the AV node and slow conduction through it. Digoxin is an alternative but is not effective in preventing exercise induced increase in heart rate. Once rate control is achieved with above drugs conversion to sinus rhythm may be attempted by DC shock or antiarrhythmic drugs (amiodarone, flecainide, or ibutilide). It is important to increase AV node refractoriness before giving antiarrhythmic drugs because their vagolytic effect and/or their ability to convert AF to atrial flutter may lead to an excessively rapid ventricular response and hemodynamic collapse. β-blockers are useful to increase the refractoriness of AV node. However, if the patient is already on anticoagulation and his prothrombin time is within therapeutic range, then cardioversion can be attempted Before attempting DC shock for atrial fibrillation of >48 hours old, make sure that there is no clot in the atria, otherwise they will embolize to systemic circulation. Transesophageal echo is the best way to rule out clot. If clot is present, patient should be anticoagulated for at least 3 weeks prior to cardioversion.
- If there is a precipitating factor such as alcohol intoxication, fever, thyrotoxicosis, etc., it should be treated.
- Antiarrhythmic drugs are not recommended to maintain sinus rhythm after converting to sinus rhythm, because the risks outweigh the benefits. However, amiodarone can be used in patients with heart failure, moderate-to-severe systolic dysfunction, or hypertension with substantial left ventricular hypertrophy.
- Most of the recent guidelines favor rate control rather than rhythm control in atrial fibrillation, i.e. no need to convert the AF into sinus rhythm, only the ventricular rate needs to be controlled.
- Chronic anticoagulation is required for these patients to prevent clot formation. Warfarin should be used to maintain INR between 2 and 3.
- Patients with poor rate control despite optimal medical therapy should be considered for AV node ablation and pacemaker implantation (*'ablate and pace' strategy*).

Q. Atrial flutter.

- Atrial flutter is an organized atrial rhythm with an atrial rate between 250 and 350 beats per minute.

Etiology

- Causes of atrial flutter are same as atrial fibrillation.

Mechanism

- Atrial flutter is due to impulses traveling through a re-entrant circuit within the right atrium and causing repeated activation of atria. Because of refractoriness of AV node all impulses are not conducted into ventricles. Typically, the ventricular rate is half the atrial rate, i.e. ~150 beats/min because of 2:1 block in the AV node.

Clinical Features

- Patients usually complain of palpitaions. Very fast heart rate due to 1:1 AV response may cause angina and hemodynamic instability.

Investigations

- *ECG* shows regular sawtooth-like atrial flutter waves (F waves) between QRS complexes.

Management

- Electrical cardioversion is the treatment of choice for acute symptomatic attack.
- If atrial flutter is more than 1–2 days old, patients should be anticoagulated for 4 weeks prior to cardioversion.
- Recurrent attacks may be prevented by antiarrhythmic drugs (amiodarone). In persistent atrial flutter ventricular rate control can be achieved by AV nodal blocking agents (β-blockers and/or calcium channel blockers).
- However, the treatment of choice for patients with recurrent atrial flutter is radiofrequency catheter ablation. Catheter ablation is superior to rate-control and rhythm-control strategies with antiarrhythmic drugs.

Q. Preexcitation syndromes.

Q. Wolff-Parkinson-White (WPW) syndrome.

- Preexcitation syndromes are due to accessory pathways between the atria and the ventricle that avoid the conduction delay of the AV node. This results in earlier activation (preexcitation) of the ventricles. Accessory pathways allow the impulses to enter into the ventricles or allow the impulses to travel back to atria thus predisposing to reentrant arrhythmias.

Lown-Ganong-Levine Syndrome

- Here the accessory pathway may be wholly or partly within the node (Mahaim fibers). Conduction occurs more rapidly than normal from the atria to the ventricles, explaining the short PR. The QRS complex is normal, since ventricular activation is via the normal conduction pathway (His Purkinje system).

Wolff-Parkinson-White Syndrome

- Here the accessory pathway (Kent bundles) directly connects the atria and ventricle. This produces a short PR interval and wide QRS complex with an early delta wave due to early ventricular depolarization of the region adjacent to the pathway. QRS is wide because the impulse to ventricles does not travel through normal conduction pathway. However, in many patients, impulse is not conducted through the bypass tract. In such cases, the bypass tract is termed "concealed" and QRS complex may be normal.
- Orthodromic tachycardia is a reentrant rhythm that conducts antegrade down the AV node and retrograde up the accessory pathway, resulting in a narrow QRS complex.
- Antidromic tachycardia conducts down the accessory pathway and retrograde through the AV node, resulting in a wide QRS complex. Up to 30% of patients with Wolff-Parkinson-White syndrome will develop atrial fibrillation or flutter with antegrade conduction down the accessory pathway and a rapid ventricular response. If this conduction is very rapid, it can potentially degenerate to ventricular fibrillation.

Investigations

- ECG
- Electrophysiological studies.

Treatment

- Disopyramide, quinidine, flecainide, and amiodarone can be used to increase the refractory period of accessory pathway and reduce conduction rate through it.
- Radiofrequency catheter ablation is the procedure of choice in patients with recurrent symptoms.

Q. Discuss the etiology, clinical features, investigations and management of atrioventricular blocks (heart blocks).

- The specialized cardiac conducting system normally ensures synchronous conduction of each sinus impulse from the atria to the ventricles. Heart block or conduction block may occur at any level in the conducting system. Block in either the AV node or the His bundle results in atrioventricular (AV) block, whereas block lower in the conduction system produces bundle branch block.

Atrioventricular Block

- AV block is defined when some or all impulses are delayed or do not reach the ventricle during normal sinus rhythm or sinus tachycardia.
- Conduction through AV node may be delayed (first degree AV block), intermittent (second-degree AV block) or absent (third-degree AV block).

First-degree AV Block

- This is simple prolongation of the PR interval to more than 0.20 seconds. Here all sinus impulses are conducted to the ventricles but with delay.

Second-degree AV Block (Intermittent AV Block)

- This occurs when some P waves conduct and others do not. It can be further divided as follows.
- ***Mobitz type I block (Wenckebach phenomenon):*** Here there is progressive PR interval prolongation until a P wave fails to conduct. Usually it does not progress to complete AV block.
- ***Mobitz type II block:*** Here the conduction fails suddenly and unexpectedly without a preceding change in PR intervals. It can progress to complete AV block. If the ventricular rate is slow and patient is symptomatic, pacemaker insertion is necessary.

Third-degree AV Block (Complete AV Block)

- Here no atrial impulse is conducted to ventricles. Usually there is escape rhythm originating either from bundle of His or ventricles. Atria and ventricles beat independently. Heart rate is usually less than 55 beats/min.
- ECG shows constant P-P and R-R intervals but with complete AV dissociation, i.e. atria and ventricles beat independently and there is no relation between P waves and QRS complexes. QRS complexes may be broad if the escape rhythm is originating from ventricles.

Table 3.38 Etiology of atrioventricular blocks

• Fibrosis and sclerosis of the conduction system	• Congenital heart disease (VSD)
• Ischemic heart disease	• Cardiomyopathies
• Drugs (digitalis, calcium channel blockers, beta blockers, amiodarone)	• Myocarditis
• Increased vagal tone	• Hyperkalemia
• Valvular disease	• Infiltrative diseases (sarcoidosis, amyloidosis)
	• Inflammatory diseases (SLE, scleroderma)

Clinical Features

- First and second degree heart blocks are usually asymptomatic.
- Third degree heart block may present with dizziness, syncope and hemodynamic instability.

Investigations

- Serum electrolytes (sodium, potassium)
- Drug levels (e.g. digoxin)
- ECG
- ECHO
- Electrophysiological testing

Treatment

- First degree heart block requires no specific treatment other than correcting the underlying cause.
- In symptomatic second and third degree heart blocks, atropine (0.5 to 2.0 mg intravenously) and isoproterenol (1 to 4 µg/min intravenously) are useful to temporarily increase the heart rate. Temporary pacemaker insertion may help stabilize the patient if there is a reversible cause such as myocardial ischemia. For long-term treatment permanent pacemaker insertion is the treatment of choice.
- Underlying cause should be identified and treated.

Q. Bundle branch blocks.

- The bundle of His divides into right and left bundle branches. The left bundle subdivides into the anterior and posterior divisions. Various conduction disturbances can occur in these bundle branches and are called bundle branch blocks.
- ***Right bundle branch block (RBBB)***: Since the right bundle branch supplies right ventricle, its block produces late activation of the right ventricle. This is manifested in ECG as deep S waves in leads I and V6 and tall late R wave in lead V1.
- ***Left bundle branch block (LBBB)***: This produces delayed activation of left ventricle which is manifested in ECG as deep S wave in lead V1 and a tall late R wave in leads I and V6.

Causes

Table 3.39 Causes of bundle branch blocks

RBBB	LBBB
• Congenital heart disease (ASD, Fallot's tetralogy, pulmonary stenosis, VSD)	• Acute myocardial infarction
• Acute myocardial infarction	• Severe coronary disease (two to three vessel disease)
• Cardiomyopathy	• Aortic stenosis
• Conduction system fibrosis	• Hypertension
• Cor pulmonale	
• Pulmonary embolism	

Clinical Features

- Bundle branch blocks are usually asymptomatic. RBBB produces widely split second heart sound. LBBB may produce reverse splitting of the second sound.

Treatment

- Usually no treatment is required. LBBB may indicate an underlying coronary artery disease which should be investigated.

Q. Define supraventricular tachycardias. List all supraventricular tachycardias.

- Supraventricular tachycardias (SVTs) are tachyarrhythmias which arise above the ventricle, i.e. from the atrium or the atrioventricular junction.
- Since the conduction is via the His-Purkinje system, QRS shape is normal (narrow QRS complex).
- Following is a list of supraventricular tachycardias:
  - Sinus tachycardia
  - Paroxysmal supraventricular tachycardias (PSVTs) (AV nodal re-entry tachycardia and AV reciprocating tachycardia)
  - Atrial fibrillation
  - Atrial flutter
  - Atrial tachycardia
  - Multifocal atrial tachycardia
  - Accelerated junctional tachycardia

Q. Paroxysmal supraventricular tachycardia (PSVT).

- PSVT is paroxysmal and recurrent and often seen in young patients with no structural heart disease. Heart rate is usually 140–220 per minute with 1:1 conduction.

Etiology

- PSVT is triggered by a reentry mechanism. This may be induced by premature atrial or ventricular ectopic beats. Other triggers include anxiety, hyperthyroidism and stimulants, including caffeine, drugs, and alcohol.
- It can be idiopathic also or rarely may be associated with congenital heart diseases such as Ebstein's anomaly, atrial septal defect, and Fallot's tetralogy.

Mechanism

- The most common mechanism for paroxysmal supraventricular tachycardia is reentry, which may be initiated or terminated by a fortuitously timed atrial or ventricular ectopic.
- The reentry circuit most commonly involves dual pathways (a slow and a fast pathway) within the AV node (known as AV nodal reentrant tachycardia (AVNRT)).
- Less commonly, reentry is due to an accessory pathway between the atria and ventricles, referred to as AV reentrant tachycardia (AVRT).

Clinical Features

- It is usually seen in young people.The first presentation is common between ages 12 and 30.
- Attacks may occur spontaneously or may be precipitated by exertion, excess coffee, tea and alcohol.
- Most common symptom of PSVT is rapid regular palpitations, usually with abrupt onset, which can occur spontaneously or precipitated by factors described above. Palpitations are usually terminated by Valsalva maneuvers.
- Other symptoms may include anxiety, dizziness, dyspnea, neck pulsation, chest pain, and weakness.
- Very fast heart rate may compromise cardiac ouput and cause hypotension and congestive heart failure.
- Polyuria may occur because of release of atrial natriuretic peptide in response to increased atrial pressures during the tachycardia.

ECG

- Rate is usually 140–220 per minute.
- P waves are not visible and are buried within the QRS complex.
- QRS complexes are narrow and occur at regular intervals.

Management

- Patients with hemodynamic instability (e.g. hypotension, pulmonary edema) require emergency cardioversion.
- If the patient is hemodynamically stable, vagal maneuvers, including right carotid massage, Valsalva maneuver, and facial immersion in cold water can be tried. Of these, Valsalva manoeuvre is the best and often easier for the patient to perform.
- If these maneuvers are not successful, intravenous adenosine (6 mg IV fast bolus) should be tried. If required, a second and third dose of 12 mg can be repeated in 1–2 minutes. Adenosine is very short-acting (half-life <10s) and causes complete heart block for a fraction of a second and terminates SVT. Side-effects of adenosine include bronchospasm, flushing, and chest pain which are transient. It is contraindicated in patients with a history of asthma.
- An alternative treatment is verapamil 5–10 mg IV over 5–10 minutes, IV diltiazem, or beta blockers (esmolol, propranolol, metoprolol).
- Verapamil, diltiazem, beta blockers or amiodarone can be given to prevent recurrence of SVT.
- Radiofrequency catheter ablation of acssesory pathway can cure SVT.

Q. Ventricular tachycardia (VT).

- VT is a rhythm which originates below the bundle of His at a rate greater than 100 beats per minute. Since it does not conduct through the normal conducting system, it is a wide-complex rhythm.
- It can be monomorphic (uniform QRS complexes) or polymorphic (QRS morphology varies).
- Sustained VT persists for 30 seconds or more. Sustained polymorphic VT is usually unstable and often degenerates into ventricular fibrillation. Sustained monomorphic VT can also degenerate into ventricular fibrillation but usually stable for long periods.
- Torsades de pointes (TdP) is a polymorphic VT with varying axis. It has a characteristic morphology ("twisting around an axis") and is associated with prolonged QT interval.

Causes

Table 3.40 Causes of ventricular tachycardia

• Ischemic heart disease • Dilated cardiomyopathy • Hypertrophic cardiomyopathy • MVP	• Myocarditis • Hypokalemia or hypomagnesemia • Drugs which prolong QT interval • Acid–base disturbance

Clinical Features

- Pulse rate is usually between 120 and 220 per min.
- Sustained VT often results in presyncope (dizziness), syncope, hypotension and cardiac arrest.

- Since the atria and ventricles beat independently, there are clinical signs of atrioventricular dissociation (cannon 'a' waves in JVP, and variable intensity of the first heart sound).

Investigations

- ***ECG***: Shows a rapid ventricular rhythm with broad QRS complexes. Supraventricular tachycardia with bundle branch block may resemble ventricular tachycardia on the ECG. However, if a broad complex tachycardia is due to SVT with either right or left bundle branch block, then the QRS morphology should resemble a typical RBBB or LBBB pattern. Since most of the cases of broad complex tachycardias are due to ventricular tachycardia, whenever there is a doubt between VT and SVT with aberrant intraventricular conduction, VT should be diagnosed and treated.
- ***Serum electrolytes***: Calcium, magnesium, sodium, potassium. Hypokalemia, hypomagnesemia, and hypocalcemia may predispose patients to either monomorphic VT or torsades de pointes.
- ***Drug levels***: For example, digoxin, toxicology screens.
- ***Serum cardiac troponin I or T levels and CK-MB***: To evaluate for myocardial ischemia or infarction.
- ***Electrophysiologic study*** is required in patients at high risk for sudden death as a result of significant underlying structural heart disease.

Treatment

- If the patient is hemodynamically unstable (hypotension, pulmonary edema, angina), emergency DC cardioversion is required.
- If hemodynamically stable, intravenous amiodarone or lidocaine can be used to terminate VT. First-line treatment consists of amiodarone (150 mg over 10 minutes, followed by 1mg/min over the next 6 hours, then 0.5 mg/min over 18 hours) or lidocaine (50–100 mg IV over 5 minutes) followed by a lidocaine infusion (2–4 mg IV per minute). DC cardioversion is necessary if medical therapy is unsuccessful.
- After resuscitation from VT, the cause of VT should be looked into and treated.

Q. Torsades de pointes.

- Torsades de pointes refers to ventricular tachycardia (VT) characterized by polymorphic QRS complexes that change in amplitude and cycle length, giving the appearance of oscillations around the baseline.

Causes

- It arises when ventricular repolarization (QT interval) is prolonged. The causes of torsades de pointes thus include causes of long QT syndrome which are as follows.
- ***Electrolyte disturbances***: Hypokalemia, hypocalcemia and hypomagnesemia.
- ***Drugs***: Phenothiazines, tricyclic antidepressants, quinidine, disopyramide, sotalol, amiodarone, macrolide antibiotics, fluoroquinolones and organophosphates.
- ***Congenital syndromes***: Jervell-Lange-Nielsen and Romano-Ward syndrome.
- ***Miscellaneous***: Bradycardia, acute myocardial infarction, liquid protein diets, dystrophia myotonica, intracranial events.
- Torsades de pointes can be precipitated by increased adrenergic drive (exertion or emotion), sudden arousal (e.g. being woken from sleep by an alarm) or it can occur even when asleep.
- In acquired long QT syndrome, QT prolongation and torsades de pointes are usually provoked by bradycardia.

Clinical Features

- Torsades de pointes causes palpitations and syncope but usually terminates spontaneously.
- It can degenerate to ventricular fibrillation and cause sudden death.

Treatment

Acute Management

- Magnesium sulphate is the drug of choice for Torsades de pointes. Magnesium is given at 1–2 g IV initially in 30–60 seconds, which then can be repeated in 5–15 minutes. Alternatively, a continuous infusion can be started at a rate of 3–10 mg/min. Magnesium is effective even in patients with normal magnesium levels.
- Any underlying precipitating factor should be addressed, i.e. correcting any electrolyte imbalances, and stopping drugs causing prolonged QT interval.
- Temporary transvenous pacing: Based on the fact that the QT interval shortens with a faster heart rate, pacing can be effective in terminating torsade.

Long Term Management

- For congenital prolonged QT interval syndrome, β-adrenergic blocking agents and drugs which shorten QT interval (phenytoin) are useful.
- ICDs with dual-chambered pacing capability have become the treatment of choice for patients with recurrent episodes in spite of using beta blockers.

Q. Ventricular fibrillation (VF).

- This is an arrhythmia characterized by disorganized electrical activity with no mechanical contraction and hence no cardiac output.

Causes

- VF occurs due to ischemic heart disease, cardiac failure, electrolyte imbalances, Brugada syndrome, etc. Ventricular ectopics during the vulnerable period of ventricular repolarization (R-on-T phenomenon) may initiate VF.

Clinical Features

- The patient is pulseless and becomes rapidly unconscious, and respiration ceases (cardiac arrest).
- ECG shows shapeless, rapid oscillations without any organized complexes.

Treatment

- VF usually ends in death within minutes unless prompt corrective measures are instituted. The rate of survival in out-of-hospital cardiac arrest has increased with expansion of community-based emergency rescue systems, widespread use of automatic external defibrillators (AEDs), and increasing numbers of laypersons trained in bystander cardiopulmonary resuscitation (CPR).
- VF rarely reverses spontaneously and requires immediate electrical defibrillation. Basic and advanced cardiac life support is needed.
- If ventricular fibrillation occurs after acute myocardial infarction, it usually does not require any prophylactic therapy. However, if the VF has occurred spontaneously without any cause, such patients are at high risk of sudden death and require implantable cardioverter defibrillators (ICDs) to prevent further attacks.

Q. Brugada syndrome.

- Brugada syndrome is an inheritable condition responsible for idiopathic ventricular fibrillation and sudden cardiac death in some patients who have no evidence of structural cardiac disease.
- It is common in young males (mean age 30 to 40 years) in South East Asia. It has autosomal dominant inheritance with variable expression. In some cases it is due to mutations in cardiac sodium channel (*SCN5A*).
- Classic ECG changes are right bundle branch block with coved ST segment elevation in leads V1–V3. These ECG changes may be present spontaneously or provoked by the administration of sodium channel blockers (flecainide or amiodarone). The QT interval is normal.
- It can present as sudden death or ventricular fibrillation or the patient may be asymptomatic and diagnosed based on ECG findings. There is a high risk of sudden death, particularly in the symptomatic patient or those with spontaneous ECG changes.
- The only successful treatment is an implantable cardioverter defibrillator (ICD). However, quinidine can be used if ICD insertion is not feasible.

Q. Classify antiarrhythmic drugs with appropriate examples.

- Antiarrhythmic drugs are agents that modify the rhythm and conduction of the heart and are used to treat cardiac arrhythmias.
- However, these drugs can also produce arrhythmias (proarrhythmia) and hence have to be used with caution.
- They are classified based on their mechanism of action as follows.

Table 3.41 Classification of antiarrhythmic drugs

		Mechanism of action	Examples
Class I		These drugs reduce maximal velocity of depolarization (V_{max}) by blocking Na^+ channels	
	IA	↓ V_{max} and prolong action potential duration	Quinidine, procainamide, disopyramide
	IB	↓ V_{max}. Decrease action potential duration	Lidocaine, phenytoin, tocainide, mexiletine
	IC	↓ V_{max} at normal rates in normal tissue. No change in action potential duration	Flecainide, propafenone, moricizine
Class II		β-blockers: ↓ SA nodal automaticity, ↑ AV nodal refractoriness, and ↓ AV nodal conduction velocity	Metoprolol, atenolol and acebutalol
Class III		These drugs prolong action potential duration in tissue with fast-response action potentials	Bretylium, amiodarone, sotalol, ibutilide, dofetilide
Class IV		Calcium (slow) channel blocking agents: ↓ conduction velocity and ↑ refractoriness in tissue with slow-response action potentials	Verapamil, diltiazem

Class I Drugs

- These drugs reduce the excitability of membrane by reducing the rate of entry of sodium into the cell (sodium-channel blockers). They may slow conduction, delay recovery, or reduce the spontaneous discharge rate of myocardial cells.
- Class I agents have been found to increase mortality compared to placebo in post-myocardial infarction patients with ventricular ectopy and inpatients treated for atrial fibrillation. In view of this, class I drugs should be avoided in patients with coronary artery disease, left ventricular dysfunction, or other forms of significant structural heart disease.

Class II Drugs

- These are antisympathetic drugs and prevent the effects of catecholamines on the action potential. Most are cardioselective beta-blockers and include metoprolol, atenolol and acebutalol.
- Betablockers suppress AV node conduction, and are effective in preventing attacks of junctional tachycardia, and are useful to control ventricular rates in supraventricular tachycardia and atrial fibrillation. They prevent ventricular fibrillation in myocardial infarction and congestive heart failure.

Class III Drugs

- These prolong the action potential and do not affect sodium transport through the membrane. Important drugs in this class are amiodarone and sotalol. Sotalol is also a beta-blocker.
- Amiodarone is the most commonly used drug. It can be used to treat atrial fibrillation, SVT, and ectopic beats. Sotalol may result in acquired long QT syndrome and torsades de pointes. Dofetilide has been used to treat atrial fibrillation and flutter in patients with recent myocardial infarction and poor LV function.

Class IV Drugs

- The nondihydropyridine calcium antagonists ↓ conduction velocity and ↑ refractoriness in tissue with slow-response action potentials and are particularly effective in slowing conduction in nodal tissue.
- These drugs can prevent attacks of junctional tachycardia (AVNRT and AVRT) and may help to control ventricular rates during atrial fibrillation.

Q. Implantable cardioverter-defibrillator (ICD).

- ICD is a device implantable inside the body, able to perform both cardioversion, defibrillation and pacing of the heart. The device is therefore capable of correcting most life-threatening cardiac arrhythmias. Life-threatening ventricular arrhythmias (ventricular fibrillation or ventricular tachycardia) can cause sudden death in up to 40% of patients within 1 year of diagnosis.
- Modern ICDs are only a little larger than a pacemaker and are implanted in the infraclavicular area. The ICD recognizes ventricular tachycardia or fibrillation and automatically delivers pacing or a shock to the heart to cause cardioversion to sinus rhythm. The device may have leads to sense and pace both the right atrium and ventricle, and the lithium batteries employed are able to provide energy for over 100 shocks each of around 30 J.
- The use of ICD has reduced the death rate to 2% per year in patients with history of serious ventricular arrhythmias or cardiac failure. Many trials have shown the superiority of ICDs in preventing sudden cardiac death compared to revascularization, antiarrhythmics, betablockers, and angiotensin-converting enzyme inhibitors.
- ICD discharges are painful if the patient is conscious. However, ventricular tachycardia may often be terminated by overdrive pacing of the heart, which is painless.
- ICDs are now first-line therapy in the secondary prevention of sudden death. Even selected patients at high risk of sudden death who have never experienced a life-threatening ventricular arrhythmia are also advised to undergo ICD implantation.
- Following are general indications for ICD insertion:
  - Spontaneous sustained VT in association with structural heart disease.
  - Nonsustained VT in patients with coronary disease, prior myocardial infarction, LV dysfunction, and inducible VT or sustained VT at electrophysiological study
  - Patients with dilated and particularly hypertrophic cardiomyopathy, long QT syndrome and Brugada syndrome who have a strong family history of sudden cardiac death.

Q. Describe the etiology, pathophysiology, clinical features, and management of pulmonary hypertension.

Definition

- Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) of equal to or greater than 25 mm Hg at rest.

Etiology

Primary Pulmonary Hypertension (PPH)

- This is present without any apparent reason.

Secondary Pulmonary Hypertension

- This is secondary to many diseases, which are as follows.

Table 3.42 Causes of pulmonary HTN

Causes of pulmonary HTN	Mechanism
Disorders of ventillation	
• Obstructive sleep apnea • Morbid obesity (Pickwickian syndrome) • Cerebrovascular disease	They produce hypoxia and pulmonary vasoconstriction leading to pulmonary HTN
Cardiac disorders	
• Mitral valve disease (stenosis and regurgitation) • Left ventricular failure • Left atrial myxoma • Congenital heart disease with Eisenmenger's reaction	They cause pulmonary HTN either by increased left atrial pressure or by increased blood flow through pulmonary circulation
Pulmonary vascular disorders	
• Acute pulmonary thromboembolism (rarely tumor emboli) • Multiple pulmonary artery stenoses • Pulmonary veno-occlusive disease • Chronic pulmonary thromboembolism • Parasitic infection, e.g. schistosomiasis	They cause increased resistance to blood flow and hence hypertension
Diseases of the lung and parenchyma	
• COPD (most common cause) • Interstitial lung diseases • Other chronic lung disorders	They decrease the surface area of pulmonary vasculature and hypoxia leading to pulmonary HTN
Musculoskeletal disorders kyphoscoliosis	
• Poliomyelitis • Myasthenia gravis	They cause chronic underventilation leading to hypoxia, pulmonary vasoconstriction and pulmonary HTN
Miscellaneous	
• Appetite-suppressant drugs, e.g. dexfenfluramine • Type 1 glycogen storage diseases • Lipid storage diseases, e.g. Gaucher's disease • Connective tissue diseases, e.g. SLE, scleroderma, sarcoidosis • Cirrhosis of liver • Sickle cell disease • HIV infection	They cause increased resistance to pulmonary blood flow and also endothelial damage leading to pulmonary HTN

Pathophysiology

- Pulmonary HTN leads to right ventricular hypertrophy and right heart failure. Right ventricular failure leads to peripheral edema. Right ventricular dilatation leads tricuspid annular dilatation leading to functional TR.

Clinical Features

Symptoms

- Patients usually present with exertional dyspnea (commonest symptom), chest pain, syncope and fatigue.
- Exertional dyspnea, fatigue and syncope are due to the inability of the heart to increase cardiac output because of decreased blood flow from right to left side of the heart. Chest pain may be due to right ventricular ischemia.
- Hemoptysis can occur due to rupture of distended pulmonary vessels.
- In addition, there can be symptoms of underlying disease causing pulmonary HTN.

Signs

- JVP is raised with a prominent 'a' wave.
- A right ventricular (parasternal) heave is present, and a loud P2 is heard.
- Other findings include a right ventricular fourth heart sound, and an early diastolic murmur due to pulmonary regurgitation (*Graham Steell murmur*). This murmur is heard over the second and third left intercostal spaces, close to the sternum.
- Tricuspid regurgitation may develop and indicates right ventricular failure. If TR develops, there is a pansystolic murmur and a large jugular 'v' wave.
- Features of right ventricular failure such as acsites, peripheral edema and hepatomegaly may be present.

Investigations

- ***Chest X-ray***: May show right ventricular and right atrial enlargement. Pulmonary arteries are enlarged and taper rapidly. There is peripheral pruning of pulmonary arteries. Peripheral lung fields are oligaemic. X-ray may also show the underlying disease causing pulmonary HTN.
- ***ECG***: Demonstrates right ventricular hypertrophy (right axis deviation, dominant R wave in lead V1, and inverted T waves in right precordial leads) and right atrial enlargement (tall peaked P waves in lead II)
- ***Echocardiography***: Shows right ventricular dilatation and/ or hypertrophy, reduction in left ventricular (LV) cavity size, and tricuspid regurgitantion. Echocardiogram may also reveal the cause of pulmonary hypertension, such as mitral stenosis or an intracardiac shunt.
- ***Other investigations***: Pulmonary function tests are helpful in documenting underlying obstructive airway disease or severe restrictive lung disease. Hypoxemia and an abnormal diffusing capacity for carbon monoxide

are common findings of pulmonary hypertension. A lung perfusion scan is helpful in evaluating thromboembolic pulmonary hypertension. ANA to identify connective tissue diseases and HIV testing should be done in unexplained pulmonary HTN. HRCT (high resolution CT) scan of lung is useful to rule out interstitial lung disease. Sleep studies are helpful to rule out obstructive sleep apnea.

Treatment

Secondary Pulmonary HTN

- This is best treated by identifying and correcting the underlying cause.

Primary Pulmonary HTN

General measures

- Patients should avoid strenuous exercise since it increases pulmonary HTN dramatically. Digoxin and diuretics are useful if there is right heart failure causing peripheral edema and ascites. Oxygen supplementation helps to decrease dyspnea and improves pulmonary hypertension.

Anticoagulant therapy (e.g. warfarin)

- This is indicated for all patients with primary pulmonary hypertension (PPH) because thrombin deposition occurs in the pulmonary circulation and serves as a growth factor to promote the disease process.

Calcium channel blockers

- These drugs are useful for patients who have reversible vasoconstriction of pulmonary vasculature (reversibility can be identified by cardiac catheterization and injecting short-acting vasodilators). High doses of calcium channel blockers are required (e.g. nifedipine, 240 mg/d, or amlodipine, 20 mg/d).

Prostaglandins

- Epoprostenol (prostacyclin) and treprostinil (an analogue of epoprostenol) are useful in treating patients who are unresponsive to other therapies. Clinical trials have demonstrated an improvement in symptoms, exercise tolerance, and survival with these drugs. Epoprostenol can only be administered intravenously and requires placement of a permanent central venous catheter and infusion through an ambulatory infusion pump system. Treprostinil can be administered subcutaneously through a small infusion pump.

Endothelin receptor antagonists

- The nonselective endothelin receptor antagonist bosentan has been shown to improve exercise tolerance and other symptoms. Orally active agents sitaxsentan and ambrisentan are under investigation. These drugs can cause increase in liver enzymes, hence liver function should be monitored monthly throughout the duration of use.

Sildenafil

- This is an oral phosphodiesterase-5 inhibitor which has vasodilator action. It dilates pulmonary arteries and lowers pulmonary vascular pressure.

Lung transplantation

- This is considered in patients who remain symptomatic in spite of all the above treatments. Acceptable results have been achieved with heart-lung, bilateral lung, and single lung transplant.

Q. Describe the etiology, clinical features, diagnosis, complications and management of deep vein thrombosis (venous thrombosis).

Q. Prophylaxis of deep vein thrombosis (DVT).

- The presence of thrombus within a superficial or deep vein and the accompanying inflammatory response in the vessel wall is termed *venous thrombosis* or *thrombophlebitis*.
- Thrombus formation within deep veins, especially of the lower limbs is termed deep venous thrombosis (DVT).

Common Sites of DVT

- Deep venous system of lower limbs (most cases of pulmonary embolism are due to this).
- Pelvic veins.

Etiology (Risk Factors)

Table 3.43 Risk factors for DVT

Inherited	Acquired
• Factor V Leiden mutation • Prothrombin gene mutation • Protein S deficiency • Protein C deficiency • Antithrombin (AT) deficiency • Dysfibrinogenemia	• Prolonged travel • Prolonged immobilization (due to surgery, fractures, stroke, illness) • Obesity • Cigarette smoking • Drugs (oral contraceptives, steroids, tamoxifen) • Pregnancy • Postmenopausal hormone replacement • Antiphospholipid antibody syndrome • Cancer • Chronic obstructive pulmonary disease (because of hypoxia induced polycythemia) • Congestive heart failure • Presence of a central venous catheter • Hyperhomocysteinemia • Myeloproliferative disorders (essential thrombocythemia, polycythemia vera) • Paroxysmal nocturnal hemoglobinuria • Inflammatory bowel disease • Nephrotic syndrome • Hyperviscosity (Waldenstrom's macroglobulinemia, multiple myeloma, leukocytosis in acute leukemia, sickle cell anemia)

3

Pathogenesis

- Virchow described three factors (Virchow's triad) in the causation of venous thrombosis. These are:
  1. Stasis of blood
  2. Abnormalities of vessel wall
  3. Hypercoagulable state
- Any one or more of the above factors may be present in DVT.

Clinical Features

- DVT may be asymptomatic in 50% of cases.
- Classic symptoms of DVT include swelling, pain, and discoloration in the involved limb. Superficial veins are dilated. Affected limb is usually warm.
- Thrombosed vein may be palpable as a cord.
- There may be pain and tenderness along the course of the affected vein.
- There may be pain in the calf on forceful dorsiflexion of the foot (Homan's sign).
- In advanced cases, there may be cyanosis and venous gangrene in the affected limb.

Table 3.44 Wells clinical prediction guide for diagnosis of DVT

Clinical Variable	Score
• Active cancer	1
• Paralysis, paresis, or recent cast	1
• Bedridden for >3 days; major surgery <12 weeks	1
• Tenderness along distribution of deep veins	1
• Entire leg swollen	1
• Unilateral calf swelling >3 cm	1
• Pitting edema	
• Previous DVT documented	11
• Collateral superficial nonvaricose veins	1
• Alternative diagnosis at least as likely as DVT	–2

Low probability = score ≤ 0, moderate probability = score 1 or 2, high probability = ≥ 3

Differential Diagnosis of DVT

- Ruptured Baker's cyst.
- Cellulitis.
- Postphlebitic syndrome/venous insufficiency.
- Calf muscle pull or tear.
- Lymphatic filariasis.

Complications

- Pulmonary embolism.
- Venous gangrene.
- Postphlebitic syndrome (edema, venous claudication, skin pigmentation, dermatitis, and ulceration).
- Chronic venous insufficiency.
- Chronic thromboembolic pulmonary hypertension.

Diagnosis of DVT

D-dimer

- D-dimer levels are elevated in DVT (more than 500 ng/mL in most patients with DVT). It is a breakdown product of fibrin and is present whenever clot formation occurs. It is more elevated in pulmonary embolism than DVT because the clot is bigger in pulmonary embolism.
- D-dimer is a useful "rule out" test. A negative D-dimer test almost rules out DVT, but a positive test has to be further investigated by Doppler ultrasonography.
- The D-dimer assay is not specific to DVT. Levels can also increase in patients with myocardial infarction, pneumonia, sepsis, cancer, the postoperative state, and second or third trimester of pregnancy.

Venous Doppler Ultrasonography

- Loss of vein compressibility with gentle manual pressure from the ultrasound transducer suggests thrombosis. Loss of compressibility is due to passive distension by thrombus.
- Thrombus may appear as homogeneous and low echogenicity mass. The vein itself often appears mildly dilated, and collateral channels may be absent.
- Other features of DVT are loss of augmentation of flow on compression and loss of normal respiratory variation. If ultrasound is inconclusive, CT or magnetic resonance imaging of veins may help.

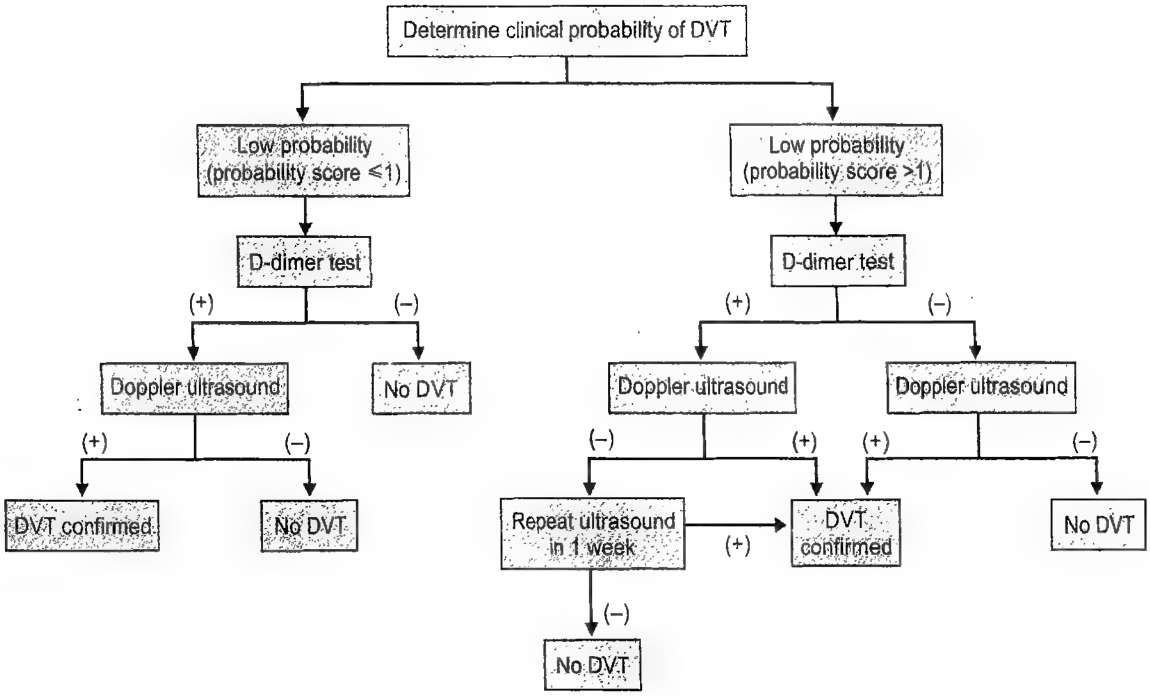
Magnetic Resonance (MR) (Contrast-Enhanced)

- When ultrasound is equivocal, MR venography is an excellent imaging modality to diagnose DVT.

Ascending Contrast Venography

- This is rarely used now because of availability of Doppler ultrasound and MR venography.

Algorithm for Diagnosing DVT



Treatment of DVT

- The objectives of DVT treatment are prevention of further clot extension, prevention of acute pulmonary embolism, reduction of recurrent thrombosis, reduction of late complications such as postphlebitic syndrome, chronic venous insufficiency, and pulmonary hypertension.

Anticoagulant Therapy

- Anticoagulation is the main treatment for DVT. Parenteral anticoagulants are used initially to achieve immediate anticoagulation. Either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) can be used for this purpose.
- ***Unfractionated heparin*:** Dose should be adjusted to achieve aPTT of 2–3 times the upper limit of normal.
- ***Low molecular weight heparins (LMWH)*:** Do not require any monitoring, convenient to use and are cost effective. They also have less chances of heparin induced thrombocytopenia (HIT).
- ***Fondaparinux*:** This is an anti-Xa pentasaccharide. It is administered as once-daily subcutaneous injection to treat DVT. No laboratory monitoring is required.
- ***Oral anticoagulation*:** Warfarin can be started on the first day itself as it takes 5–7 days for its effect to come. During this 5–7 days period, heparin and oral agents are overlapped. After 5–7 days heparin can be discontinued and warfarin continued. Usual starting dose of warfarin is 5–10 mg. it should be adjusted to achieve a target INR of 2.0–3.0.
- Anticoagulation should be continued for 3–6 months if there is a reversible risk factor. For idiopathic DVT, anticoagulation should be given for 6–12 months. For patients at risk of recurrent DVT (e.g. hypercoagulable disorders), anticoagulation should be given indefinitely.

Inferior Vena Caval (IVC) Filters

- IVC filter is helpful to prevent pulmonary embolism. It is indicated when anticoagulation is contraindicated because of active bleeding and in recurrent venous thrombosis despite intensive anticoagulation.

Elastic Compression Stocking

- Use of an elastic compression stocking for first 2 years prevents postphlebitic syndrome. It should be used as soon as DVT is diagnosed. Stockings need not be worn when patient is in bed.

Leg Elevation

- Elevation of affected leg to 15 degrees reduces pain and edema.

Early Ambulation

- Once anticoagulation has been started and the patient's symptoms (i.e. pain, swelling) are under control, patient is encouraged to ambulate.

Prophylaxis of Deep Vein Thrombosis

- DVT prophylaxis is indicated in patients at high risk of developing DVT. Such patients are as follows:

Table 3.45 Indications for DVT prophylaxis

High risk surgical patients	High risk medical patients
• Fracture of pelvis or lower limb bones • Hip and knee joint replacement • Major abdominal and gynecologic surgery • Multiple trauma • Acute spinal cord injury	• Acute coronary syndrome • Cardiac failure • Active cancer • Sepsis • ARDS • Severe infections (pneumonia) • Stroke • Paraplegia • Patients on mechanical ventilator

- Measures useful for DVT prophylaxis are as follows:
  - Limb physiotherapy.
  - Early mobilization.
  - Graduated compression stockings.
  - Intermittent pneumatic compression devices to both legs.
  - Unfractionated heparin, 5000 units subcutaneously 12th hourly or low molecular weight heparin subcutaneously.
  - All the above methods can be combined in high risk patients.
  - Oral warfarin after initial heparin therapy if the risk factor perists for a long time.

Q. What is pulmonary embolism?

Q. Discuss the etiology, pathophysiology, clinical features, diagnosis, and management of acute pulmonary embolism.

Definition

- Pulmonary embolism (PE) refers to exogenous or endogenous material traveling to the lungs blocking pulmonary artery or its branches.
- This leads to a potential spectrum of consequences, including dyspnea, chest pain, hypoxemia, and sometimes death.

Types

- Massive pulmonary embolism
- Small peripheral artery embolism
- Multiple recurrent pulmonary emboli

Etiology and Risk Factors

- Etiology of pulmonary thromboembolism is same as that of DVT.
- Thrombus from deep veins of lower limbs is the most common material embolizing to the lungs. Emboli can also occur from tumor, fat (long bone fractures), amniotic fluid, and foreign material during IV drug abuse.
- The following discussion refers to pulmonary embolism due to deep vein thrombosis.

Pathophysiology

- After pulmonary embolism, lung tissue is ventilated but not perfused—producing an intrapulmonary dead space and impaired gas exchange. After a few hours, the non-perfused lung no longer produces surfactant leading to alveolar collapse, which exacerbates hypoxaemia.
- Pulmonary embolism causes a reduction in the cross-sectional area of the pulmonary arterial bed leading to elevation of pulmonary arterial pressure and dilatation of right ventricle and right atrium.
- A massive pulmonary embolism obstructing the main branches of pulmonary artery may cause sudden hemodynamic collapse and death.
- Embolism into a small peripheral artery may produce pulmonary infarction leading to hemoptysis and pleuritic chest pain. Infarction may not always occur because oxygen continues to be supplied by the bronchial circulation and the airways.

Clinical Features

Massive Pulmonary Embolism

- This leads to sudden hemodynamic collapse due to acute obstruction of the right ventricular outflow.
- Patients present with hypotension and shock.
- Central chest pain may be complained of due to cardiac ischemia due to lack of coronary blood flow.
- Syncope and sudden death may occur due to sudden reduction in cardiac output.
- On examination, the patient appears pale, sweaty and tachypnoeic.
- Tachycardia and hypotension are usually present.
- JVP is raised with a prominent *'a'* wave due to right heart failure.
- There is a right ventricular heave, a gallop rhythm and a widely split second heart sound because P2 is delayed due to right ventricular failure. Tricuspid regurgitation murmur may be present due to right ventricular dilatation.

Small Peripheral Artery Embolism

- This leads to sudden onset of dyspnea, pleuritic chest pain, and hemoptysis. Chest pain and hemoptysis are due to pulmonary *infarction*.
- Other symptoms are palpitations, cough, anxiety, and lightheadedness.

- Many pulmonary emboli occur silently without any symptoms.
- On examination, the patient may be tachypnoeic with a localized pleural rub and often coarse crepitations over the area involved. Pleural effusion can develop on the affected side.

Multiple Recurrent Pulmonary Emboli

- This leads to insidious onset breathlessness, over weeks to months and pulmonary HTN.
- Patient has symptoms of pulmonary HTN such as exertional dyspnea, weakness, exertional syncope, and occasionally angina.
- On examination, there are signs of pulmonary HTN such as right ventricular heave and loud P2.

Evidence of Deep Vein Thrombosis

- Erythema, warmth, pain, swelling, or tenderness may be present in one or both legs.
- Pain with dorsiflexion of the foot (Homans' sign) may also be present.

Wells Scoring System

- This is used to determine the probability of pulmonary embolism (PE)

Table 3.46 Wells scoring system

Clinical variable	Score
• Signs and symptoms of DVT	3.0
• Alternative diagnosis less likely than PE	3.0
• Heart rate >100/min	1.5
• Immobilization >3 days; surgery within 4 weeks	1.5
• Prior PE or DVT	1.5
• Hemoptysis	1.0
• Malignancy present	1.0

Clinical probability of PE: High if score >6; intermediate if 2–6; low if <2

Differential Diagnosis

- Since the symptoms and signs of pulmonary embolism are non-specific, other diagnoses with similar presentation should be kept in mind. These are
- Acute coronary syndrome, including unstable angina and acute myocardial infarction
- Pneumonia
- Acute exacerbation of asthma or COPD
- Congestive heart failure
- Pericarditis
- Pneumothorax
- Primary pulmonary hypertension
- Anxiety with hyperventilation.

Diagnosis

D-dimer

- Is elevated (>500 ng/ml) in more than 90% of patients with pulmonary embolism (PE). D-dimer is a product of endogenous fibrin breakdown and indicates presence of clot in the vascular system.
- It is not specific for PE because it is also positive in myocardial infarction, sepsis, or almost any systemic illness. However, it has high sensitivity of 96% and a negative predictive value of 99%.
- If D-dimer is negative, it essentially rules out PE. If it is positive, PE must be confirmed by other tests.

ABG (Arterial Blood Gas) Analysis

- Usually shows hypoxemia and low arterial CO_2 level, i.e. type 1 respiratory failure pattern.

ECG

- Sinus tachycardia; new-onset atrial fibrillation or flutter.
- S1-Q3-T3 pattern (S wave in lead I, Q wave in lead III, and an inverted T wave in lead III).
- Right axis deviation and right ventricular strain (T-wave inversion in leads V_1 to V_4).
- ECG is also useful to rule out other diagnoses such as myocardial infarction.

Chest X-ray

- Common radiographic findings include pleural effusion, atelectasis, pulmonary infiltrates, and mild elevation of hemidiaphragm.
- Classic signs of pulmonary infarction, such as Hampton's hump (wedge-shaped opacity above the diaphragm with base towards pleura) or decreased vascularity (Westermark's sign) may be present.
- Dilatation of pulmonary artery and right ventricle.
- Abrupt cut-off of a vessel.
- Chest X-ray is also useful to rule out other diagnoses such as pneumothorax, pneumonia or rib fracture.

Doppler Ultrasound

- This is done to detect thrombosis of pelvic, iliofemoral or calf veins.

Echocardiography

- May reveal abnormalities of right ventricular size or function that may support the diagnosis of pulmonary embolism. It can occasionally show the clot in the proximal pulmonary arteries.

Ventilation-perfusion Scanning (V/Q Scan)

- This is a very good test, but nowadays is being replaced by CT-angiogram. V/Q scanning may be used when CT scanning is not available or if the patient has a contra-indication to CT scanning or intravenous contrast material.
- Perfusion scan is obtained by 99mTc scintigraphy which demonstrates underperfused areas. Ventilation scan is obtained by inhalation of radioactive xenon gas. If there is a perfusion defect in the normally ventilated area, it is highly suggestive of a pulmonary embolism.
- However, there are some limitations to the test. For example, a similarly matched defect may be seen in emphysematous bulla. Hence, this test should be interpreted in the context of the history, examination and other investigations.

CT-angiogram and MR-angiogram

- CT-scans with intravenous contrast (CT pulmonary angiography) show good sensitivity and specificity for medium-sized pulmonary emboli. New multislice CT machines have high sensitivities for even very small thrombi. MR imaging gives similar results and is used if CT angiography is contraindicated.

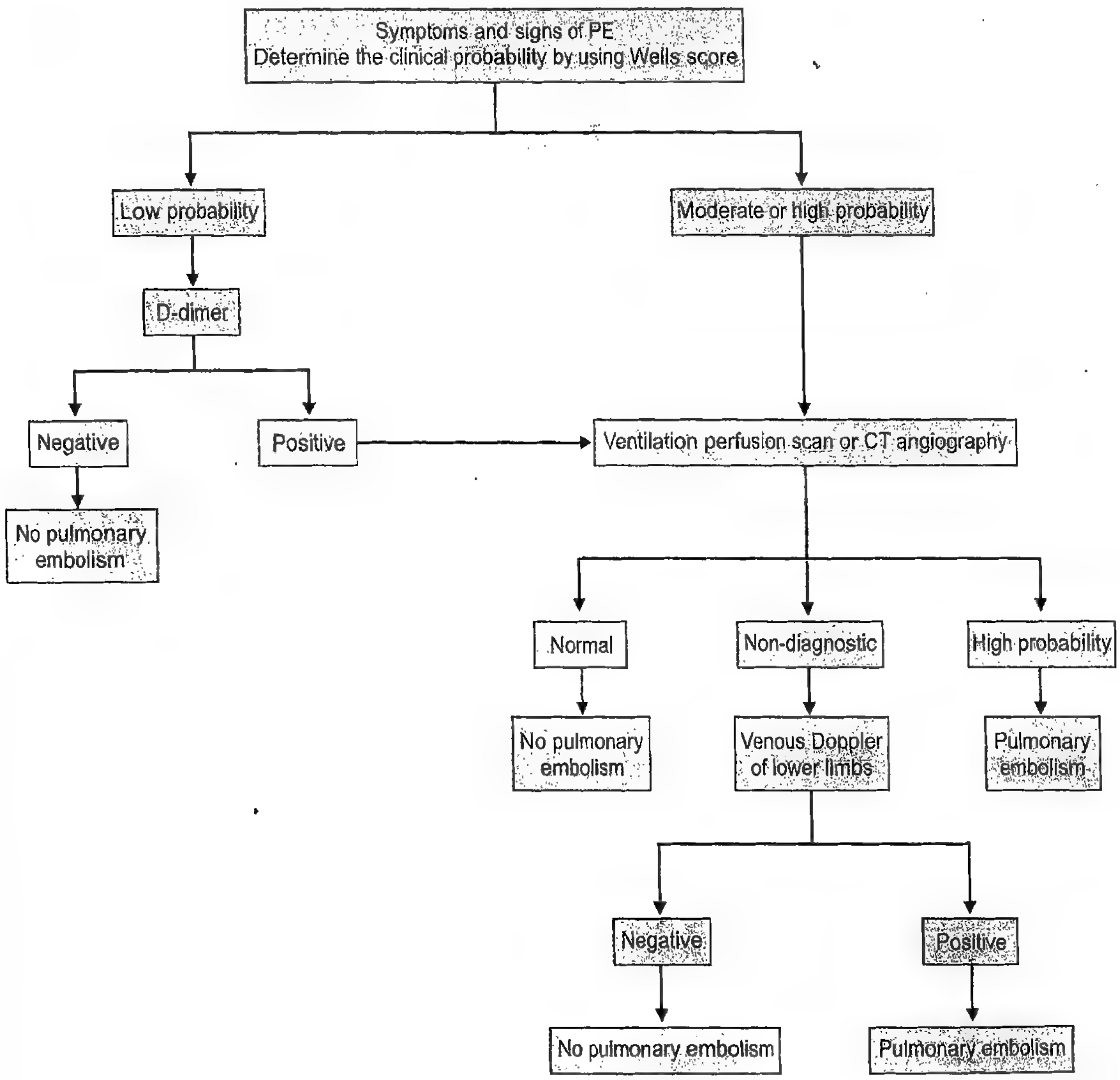
Pulmonary Angiography

- This has remained the accepted "gold standard" technique for the diagnosis of acute pulmonary embolism. It is an extremely sensitive, specific, and safe test. Nowadays it is done only if surgery is considered in acute massive embolism. The test is performed by injecting contrast material through a catheter inserted into the main pulmonary artery. Filling defects or obstructed vessels can be visualized.

Other Tests

- Troponin levels are usually elevated in pulmonary embolism due to right ventricular damage.

Algorithm for the Diagnosis of Pulmonary Embolism



Treatment

General Measures

- High-flow oxygen (60–100%) should be given to all patients. All patients should be admitted to intensive care unit. Intravenous fluids and inotropic agents (dopamine and noradrenaline) should be started if there is hypotension. Intubation and mechanical ventilation should be considered in all patients if there is respiratory compromise.

Anticoagulation

- Anticoagulants prevent the progression of thrombus and further emboli.
- Either low-molecular-weight heparin (LMWH) (e.g. dalteparin, enoxaparin) or unfractionated heparin can be used for this purpose. Unfractionated heparin is given at an initial dose of 5000–10,000 units intravenously, followed by continuous infusion of 1000 units per hour.
- LMWHs have the advantage of less frequent dosing, and aPTT need not be monitored. The chances of heparin induced thrombocytopenia (HIT) is also less with LMWHs.
- Oral anticoagulants (warfarin) are usually begun immediately and the heparin is tapered off after 5–7 days of overlap as the oral anticoagulant becomes effective. Oral anticoagulants are continued for 6 weeks to 6 months, depending on the likelihood of recurrence of venous thrombosis or embolism. Lifelong anticoagulation is indicated in recurrent embolism.
- If the patient develops HIT, direct thrombin inhibitors such as dabigatran, rivaroxaban and lepirudin can be used instead of heparin. Bleeding due to excess heparin can be corrected by injecting protamine sulphate and due to warfarin by injecting vitamin K.

Thrombolytic Therapy

- In addition to anticoagulation, thrombolytic therapy is also indicated in patients with massive pulmonary embolism with hemodynamic compromise such as hypotension. Streptokinase (2.5 lakh units by IV infusion over 30 minutes, followed by 1 lakh units IV hourly for up to 12–72 hours) or urokinase or tPA (tissue plasminogen activator) can be used for thrombolysis. Thrombolysis has been shown to clear pulmonary emboli more rapidly and to confer a survival benefit in massive PE.

Surgery

- Surgical pulmonary embolectomy may be appropriate in patients who have massive embolism occluding the main or proximal branches could be considered in all patients if they are not able to mantain and cannot receive thrombolytic therapy.

Vena Caval Filters

- Indications for IVC filter placement include contraindications to anticoagulation and recurrent embolism while on anticoagulant therapy. IVC filters are sometimes placed in the setting of massive PE when it is believed that any further emboli might be lethal, particularly if thrombolytic therapy is contraindicated. Greenfield filter has been most widely used. Filters can be inserted via the jugular or femoral vein.

Prevention of Pulmonary Embolism

- This is same as prophylaxis for DVT.

Q. Nonthrombotic pulmonary embolism.

- Pulmonary embolism can also result from substances other than thrombus. These include fat, air, amniotic fluid, and foreign bodies.

Fat Embolism

- Fat embolism usually occurs in the setting of fracture of long bones and major surgery. Trauma to other fat-rich tissues such as the liver or subcutaneous tissue can occasionally result in fat embolism.
- The fat particles which enter into vascular system cause obstruction of multiple vessels. Free fatty acids released from neutral fat by lipases cause diffuse vasculitis with capillary leakage from cerebral, pulmonary, and other vascular beds.
- Symptoms develop 24 to 48 hours after the event which include a characteristic syndrome of dyspnea, petechiae, and mental confusion.
- The diagnosis is made from the clinical and radiographic findings in the setting of risk factors such as surgery or trauma. Fat droplets (by oil red O stain) may be found in bronchoalveolar lavage fluid in fat embolism. However, the diagnosis of fat embolism remains a diagnosis of exclusion.
- Treatment is supportive, including oxygen and mechanical ventilation, and the prognosis is generally good.

Amniotic Fluid Embolism

- Although uncommon, amniotic fluid embolism is one of the causes of maternal death during or after delivery. The delivery may be either spontaneous or by cesarean section and usually without any complication.
- Amniotic fluid may gain access to uterine venous channels during or after delivery. It then travels to pulmonary and general circulations. Amniotic fluid has thromboplastic activity and leads to extensive fibrin deposition in the pulmonary vasculature and other organs.

A severe consumptive coagulopathy ensues, with marked hypofibrinogenemia. After the acute event, an enhanced fibrinolytic state often develops. ARDS develops frequently.

- Clinical features are sudden onset dyspnea. There may be hypotension and death can occur. Left ventricular dysfunction may occur, due to the myocardial depressant effect of amniotic fluid.
- Examination of the pulmonary arterial blood may reveal the amorphous fragments of vernix caseosa, squamous cells, or mucin.
- Treatment is supportive, with oxygen, mechanical ventilation, and inotropes. Administration of heparin, antifibrinolytic agents such as ε-aminocaproic acid, and cryoprecipitate may be useful in selected patients.

Air Embolism

- Air embolism occurs when large amount of air gains access into the venous system.
- The incidence has increased due to frequent invasive surgical and medical procedures, frequent use of indwelling venous and arterial catheters, and the frequency of thoracic and other forms of trauma.
- Air embolism may be asymptomatic or result in death if severe. If there is patent foramen ovale, air can cross from right to left side and result in systemic embolization. In the absence of a patent foramen ovale, lungs filter most of the air, but large amount of air can still gain access to the systemic circulation.
- Symptoms include dyspnea, wheezing, chest pain, cough, agitation, confusion, tachycardia, hypotension and seizures. A "mill wheel murmur" due to air in the right ventricle may sometimes be heard.
- Arterial blood gas analysis reveals hypoxemia and hypercapnia in severe cases. Chest X-ray may show pulmonary edema or air fluid levels.
- Treatment includes immediate placement of the patient in the Trendelenburg/left lateral decubitus position and administration of 100% oxygen. If air is present in the right side of the heart, it should be aspirated by a central venous catheter. Occasionally, hyperbaric oxygen is indicated. Anticonvulsants are given to control seizures.

Q. Define and classify hypertension. Describe the etiology, pathophysiology, clinical features, diagnosis, and management of essential hypertension.

Q. Joint national committee VII (JNC-VII) classification of blood pressure.

Q. Secondary hypertension.

- Hypertension is defined as a systolic blood pressure (SBP) of 140 mm Hg or more, or a diastolic blood pressure (DBP) of 90 mm Hg or more, or taking antihypertensive medication. Normal BP is less than 140/90 mm Hg.
- The earlier classsicfication of hypertension as prehypertension, stage-1 and stage-2 hypertension has been removed now.
- Hypertension is a major cause of premature atherosclerosis leading to cerebrovascular events, ischemic heart disease and peripheral vascular disease.
- Hypertension is very common in the developed world and is present in 20–30% of the adult population. Hypertension rates are much higher in black Africans (40–45% of adults). The risk of mortality or morbidity rises progressively with increasing systolic and diastolic pressures.
- BP should be measured at least twice at different times before classifying a patient as hypertensive. Blood pressure should be measured at least twice after 5 minutes of rest with the patient seated, the back supported, and the arm at heart level. The cuff should not be too small for the arm, and tobacco and caffeine should be avoided for at least 30 minutes before measuring BP.
- When assessing the cardiovascular risk, the average blood pressure at separate visits is more accurate than measurements taken at a single visit.

Types of Hypertension

Primary HTN (Essential HTN)

- Here, a single reversible cause of hypertension cannot be identified. Primary HTN accounts for the majority (95%) of cases of HTN. The term "essential hypertension" was used earlier because it was thought that progressive increase in blood pressure with advancing age was essential to maintain blood flow through atherosclerotic arteries.

Secondary HTN

- Here, a definite reason for hypertension can be found such as renal disease, endocrine problems, etc.

Etiology of Hypertension

Primary HTN (essential HTN, idiopathic HTN)

- There are many risk factors for essential hypertension.

Genetic Factors

- Blood pressure tends to run in families and children of hypertensive parents tend to have higher blood pressure than age-matched children of people with normal blood pressure. Concordance of blood pressure is greater within

families than in unrelated individuals, greater between monozygotic than between dizygotic twins. However, the exact genetic loci and mutations are unknown.

Gender and Ethnicity

- Before age 50, the prevalence of hypertension is lower in women than in men, probably due to a protective action of estrogen. After menopause, the prevalence of hypertension increases rapidly in women and exceeds that in men. African Americans have higher prevalence of hypertension than other races.

Obesity

- Fat people are more prone to develop hypertension than thin people. The underlying mechanisms by which obesity leads to hypertension are incompletely understood, but there is mounting evidence for an expanded plasma volume plus sympathetic overactivity.

Alcohol Intake

- People who consume large amount of alcohol have higher blood pressure than those who do not drink. However, small amount of alcohol intake is actually associated with lower blood pressure.

Sodium Intake

- High sodium intake is associated with hypertension. Studies of the restriction of salt intake have shown a beneficial effect on blood pressure.

Stress

- Acute stress can temporarily raise blood pressure. However, the relationship between chronic stress and blood pressure remains to be proven.

Humoral Mechanisms

- Abnormalities in the autonomic nervous system, and renin—angiotensin system have been also implicated in the pathogenesis of essential HTN. Some hypertensive patients have been defined as having low-renin and others as having high-renin essential hypertension based on plasma renin activity. However, there is no convincing evidence that the above systems are directly involved in the maintenance of hypertension.

Insulin Resistance

- Insulin resistance and/or hyperinsulinemia have been suggested as being responsible for the increased arterial pressure in some patients with hypertension. A syndrome called the 'metabolic syndrome' has been described which consists of hyperinsulinemia, glucose intolerance, reduced levels of HDL cholesterol, hypertriglyceridaemia and central obesity in association with hypertension.

Table 3.47 Causes of secondary HTN

• Renal causes	Renal artery stenosis, glomerulonephritis, polycystic kidney disease, acute and chronic renal failure
• Endocrine causes	Pheochromocytoma, hypothyroidism, hyperthyroidism, Cushing's syndrome, Conn's syndrome, acromegaly, hyperparathyroidism, congenital adrenal hyperplasia
• Drugs	Oral contraceptives, steroids, NSAIDs, sympathomimetics (phenylephrine, phenylpropanolamine)
• Miscellaneous	Coarctation of aorta, obstructive sleep apnea, pre-eclampsia and eclampsia

Pathophysiology

- If hypertension remains uncontrolled for a long time, many changes take place in blood vessels and various organs.
- The resistance vessels (the small arteries and arterioles) show structural changes in the form of increased wall thickness and reduced lumen diameter. The number of these resistance vessels may also decrease. These changes result in an increased peripheral vascular resistance.
- In large arteries, there is thickening of the media, increase in collagen and deposition of calcium. These changes result in loss of arterial compliance, leading to a more pronounced arterial pressure wave. Over a period of time atherosclerotic changes develop in large arteries due to mechanical stress and endothelial injury.
- Left ventricular hypertrophy develops due to increased left ventricular load (increase in afterload). Left ventricular failure can happen in long standing uncontrolled HTN.
- Thickening and atherosclerotic changes in blood vessels supplying various organs results in damage to those organs. Changes in the renal vasculature lead to a reduced renal perfusion, reduced glomerular filtration rate and, finally, a reduction in sodium and water excretion. Changes in blood vessels of brain may lead to stroke. Changes in blood vessels of heart may lead to myocardial infarction.

Clinical Manifestations

Symptoms

- Hypertension has been termed the "silent killer," because it hardly produces any symptoms. If it is undetected in this long asymptomatic phase, it damages the heart, brain, kidneys, and blood vessels.
- Headache may be a complaint in hypertension, but usually rare and episodes of headaches do not correlate with fluctuations in ambulatory blood pressure.

- Attacks of sweating, headache, and palpitations may point towards the diagnosis of phaeochromocytoma.
- Sometimes patients may experience epistaxis when BP is very high.
- Breathlessness may be present due to left ventricular hypertrophy, diastolic dysfunction, or heart failure.
- Angina and leg claudication may be experienced due to atherosclerotic narrowing of coronary and lower limb arteries.
- Malignant hypertension may present with severe headache, vomiting, visual disturbances, seizures, altered sensorium, or symptoms of heart failure.

Signs

- BP is elevated (≥140/90 mm Hg).
- Signs of an underlying cause should be sought, such as renal artery bruits in renovascular hypertension, or radiofemoral delay in coarctation of the aorta.
- Cardiac examination reveals left ventricular hypertrophy and a loud A2.
- Enlarged, palpable kidneys may be found in polycystic kidney disease.
- A bruit may be heard over the abdomen in lumbar area in renal artery stenosis.
- Nonpitting edema, hoarse voice, and coarse skin may be present in hypothyroidism.
- Cushingoid features (lemon on stick appearance may be present in Cushing's syndrome).
- Optic fundus should be examined in all patients for hypertensive retinopathy changes. In malignant hypertension, there is papilledema.

Complications of Hypertension

- Hypertension is associated with a number of serious adverse effects.

Cardiovascular Complications

- Coronary artery disease (angina, myocardial infarction)
- Heart failure
- Left ventricular hypertrophy and sudden cardiac death
- Aortic aneurysm
- Aortic dissection
- Premature atherosclerosis of blood vessels.

Central Nervous System Complications

- Transient ischemic attacks
- *Stroke*: Hypertension is the most common and most important risk factor for stroke.
- Intracerebral hemorrhage
- Subarachnoid hemorrhage
- Hypertensive encephalopathy: This is characterized by very high blood pressure, papilledema, blurring of vision, headache, altered sensorium and focal neurological deficits.

Renal Complications

- Proteinuria
- Chronic renal failure: Hypertension is a risk factor for an end-stage renal disease.
- Hypertensive nephrosclerosis
- Hypertension can accelerate the progression of a variety of underlying renal diseases.

Ophthalmic Complications

- Arteriolosclerosis—localized or generalized narrowing of vessels
- Copper wiring and silver wiring of arterioles as a result of arteriolosclerosis (See Assessment)
- Arteriovenous (AV) nicking as a result of arteriolosclerosis
- Retinal hemorrhages
- Nerve fiber layer losses
- Increased vascular tortuosity
- Remodeling changes due to capillary nonperfusion, such as shunt vessels and microaneurysms
- Choroidal damage

Malignant Hypertension

- This is characterized by very high blood pressure with papilledema and end organ damage

Investigations

Routine Tests

- Urea, creatinine and electrolytes (to assess renal function).
- Urine examination for protein and blood.
- Lipid profile.
- Blood glucose (to rule out diabetes).
- ECG usually shows evidence left ventricular hypertrophy.
- Chest X-ray usually shows cardiomegaly and rib notching if there is coarctation of aorta.

Additional Tests (Done Only if Required)

- Renal artery Doppler may be indicated if renovascular hypertension is suspected.
- 24 hour urinary cortisol and VMA is indicated if there is clinical suspicion of Cushings and phaeochromocytoma.
- T3, T4 and TSH, if hypo- or hyperthyroidism is suspected.
- Growth hormone levels and skull X-ray if acromegaly is suspected.

- Ultrasound abdomen if polycystic kidney or other renal problems are suspected.
- Ambulatory blood pressure monitoring is used to monitor blood pressure throughout the day. For this, an automatic BP measuring device is worn by the patient throughout the day. It is useful to confirm the diagnosis of hypertension in patients with 'white -coat' hypertension. These devices can also be used to monitor the response of patients to drug treatment and, in particular, can be used to determine the adequacy of 24-hour control with once-daily medication.

Treatment

General Measures

- *Weight reduction*: BMI should be <25 kg/m^2.
- *Diet*: Low fat, low sodium diet (<6 g sodium chloride per day). Fruit and vegetable consumption should be increased.
- *Habits*: Alcohol consumption should be cut down and smoking should be stopped.
- *Exercise*: Regular exercise, preferably aerobic type for at least 30 minutes per day.
- Relaxation techniques, yoga, meditation.

Antihypertensive Agents

- Antihypertensive drugs should be started if blood pressure is 150/90 mm Hg or higher in adults 60 years and older, or 140/90 mm Hg or higher in adults younger than 60 years.
- In patients with hypertension and diabetes, drugs should be started if blood pressure is 140/90 mm Hg or higher, regardless of age.
- Initial antihypertensive treatment should include a thiazide diuretic or calcium channel blocker or ACE inhibitor or ARB or betablocker. There are reports that beta blockers increase the risk of stroke. Hence, other antihypertensive agents should be preferred over beta blockers.
- Initially treatment should be initiated with one drug. This drug is increased to maximum tolerated dose gradually till BP is in the desirable range.
- If BP is not controlled within one month with a single drug, addition of a second drug should be considered. Most patients will require a combination of anti-hypertensive drugs to achieve the recommended targets.
- An easy way to remember the antihypertensive drugs is the pneumonic "ABCD" (A = ACE inhibitor or angiotensin receptor blocker, B = beta blocker, C = calcium channel blocker, D = diuretics).

ACE (Angiotensin Converting Enzyme) Inhibitors

- Examples are captopril, ramipril, enalapril, perindopril, and lisinopril.
- These drugs block the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor. They also block the degradation of bradykinin, a potent vasodilator.

Compelling Indications

- Diabetics with nephropathy: ACE inhibitors slow the progression of diabetic nephropathy and decrease proteinuria.
- Ischemic heart disease: All patients with IHD should be put on ACE inhibitors because these drugs have been shown to reduce long-term mortality and morbidity of IHD.

Contraindications

- Bilateral renal artery stenosis
- Preexisting renal failure

Side Effects

- Hypotension following the first dose
- Deterioration of renal function in those with severe bilateral renovascular disease
- Dry cough due to their effect on bradykinin.
- Angioneurotic edema

Angiotensin II Receptor Blockers (ARBs)

- *Examples*: Losartan, candesartan, valsartan, irbesartan, telmisartan and olmesartan.
- These drugs block angiotensin II receptors. Their mechanism of action is same as ACE inhibitors but, since they do not have any effect on bradykinin, they do not cause cough. They can be used instead of ACE inhibitors especially those who cannot tolerate ACE inhibitors because of persistent cough. Angioneurotic edema and renal dysfunction are also less common with these drugs than ACE inhibitors.
- Compelling indications, contraindications and side effects are same as those of ACE inhibitors.

Beta Blockers

- *Examples*: Atenolol, metoprolol, bisoprolol, oxprenolol, nebivolov, pindolol, carvedilol, propranolol and labetalol.
- These drugs act by inhibiting sympathetic and renin-angiotensin systems. They reduce the force of cardiac contraction, as well as resting and exercise-induced increase in heart rate. Beta blockers differ among themselves in terms of cardioselectivity, intrinsic sympathomimetic activity and lipid solubility. Some are

cardioselective (e.g. metoprolol and bisoprolol), some have intrinsic sympathomimetic activity and cause less bradycardia (e.g. oxprenolol and pindolol). Some are more lipid soluble and produce CNS side effects like depression (propranolol), while some are less lipid soluble (atenolol).

Compelling Indications

- *Ischemic heart disease*: Beta blockers have been shown to improve the symptoms of angina and heart failure and reduce long-term mortality and morbidity in these patients. Hence, any patient having IHD and HTN should be put on beta blockers if BP is uncontrolled even after starting ACE or ARBs.

Contraindications

- Asthma and COPD
- Peripheral vascular disease
- Heart block
- Diabetes (a relative contraindication because beta-blockers can mask hypoglycemia symptoms)

Side Effects

- Bronchospasm, bradycardia, fatigue, bad dreams, depression (propranolol) and hallucinations.

Calcium-Channel Blockers

- *Examples*: Nifedipine, amlodipine, s-amlodipine, felodipine.
- These agents reduce BP by causing arteriolar dilatation, and some (verapamil, diltiazem) also reduce the force of cardiac contraction.

Side Effects

- Headache, pedal edema, flushing. All these side effects are common with short acting agents such as nifedipine. Verapamil and diltiazem may worsen heart failure.

Diuretics

- *Examples*: Chlothalidone, hydrochlorthiazide, frusemide.
- Diuretics act by enhancing sodium excretion from the body.

Compelling Indications

- Renal failure with fluid retention
- Heart failure with fluid retention.

Side Effects

- Increased serum cholesterol, impaired glucose tolerance, hyperuricemia, and hypokalemia. All these are common with higher doses of thiazide diuretics.

Alpha Blockers

- *Examples*: Prazosin, doxazosin, terazosin, tamsulosin.
- These agents block the action of norepinephrine on alpha receptors resulting in vasodilatation and BP reduction.

Compelling Indications

- Patients having urinary obstructive symptoms due to benign prostate hyperplasia (BPH) along with hypertension will especially benefit from these drugs. They control BP as well as BPH symptoms.

Side Effects

- Postural hypotension

Direct Vasodilators

- *Examples*: Hydralazine, and minoxidil.
- These drugs relax vascular smooth muscle and cause vasodilation thus reducing the BP. These drugs are used for patients resistant to other forms of treatment.

Side Effects

- Hydralazine can cause reflex tachycardia, fluid retention and a systemic lupus erythematosus-like syndrome. Minoxidil can cause edema and excessive hair growth.

Centrally Acting Drugs

- *Examples*: Reserpine, methyldopa and clonidine.
- These drugs stimulate α_2-adrenergic receptors in the CNS lowering central sympathetic outflow. These drugs are used as add on therapy in hypertensives not responding to combinations of other drugs. Methyldopa and clonidine are especially useful in pregnant women with preeclampsia.

Side Effects

- These drugs should not be combined with beta-blockers, because both drugs together can produce bradycardia. They can cause depression. Rebound hypertension is a problem with these agents especially clonidine. α-methyldopa can cause autoimmune hemolytic anemia, lupus erythematosus and liver damage.

Contraindications

- Depression is a contraindication to centrally acting sympatholytic agents.

Treatment of Underlying Cause in Secondary Hypertension

- Surgery for pheochromocytoma, correction of renal artery stenosis, treatment of any endocrine disorder, etc.

Q. Hypertensive emergency (malignant hypertension) and hypertensive urgency.

Hypertensive Emergeny

- *Hypertensive emergeny* is acute, severe elevation in blood pressure associated with target organ damage. Patients with hypertensive emergency usually present with a blood pressure of more than 180/120 mm Hg, though there is no specific threshold since individuals who develop an acute rise in blood pressure (even if less than 180/120) can develop target organ damage if the previous pressure was normal. Earlier terms such as malignant hypertension and accelerated hypertension are not being used now.
- Target-organ damage includes hypertensive encephalopathy, preeclampsia and eclampsia, acute left ventricular failure with pulmonary edema, myocardial ischemia, acute aortic dissection, and renal failure. Damage is rapidly progressive and often fatal. The characteristic vascular lesion is fibrinoid necrosis of arterioles and small arteries, which causes the clinical manifestations of end-organ damage.
- Investigations to be done include ECG, urinalysis, serum BUN and creatinine, and CT head for patients with neurologic symptoms or signs.
- Hypertensive emergency requires ICU admission and lowering of blood pressure by intravenous medications. Sodium nitroprusside infusion is the drug of choice for hypertensive emergencies. Clevidipine is a new, ultra-short-acting (within 1 to 2 minutes), 3rd-generation Ca channel blocker that reduces peripheral resistance without affecting venous vascular tone and cardiac filling pressures. In recent trials, it has been shown to be more effective with lower mortality than nitroprusside. Starting dose is 1 to 2 mg/h, doubling the dose every 90 sec until approaching target BP. Hence, if clevidipine is available, it is the drug of choice and is preferred over sodium nitroprusside. Other alternatives are nitroglycerin or labetalol infusion. Blood pressure should be lowered gradually over many hours to a target of 170/110 mm. In the next 48 hours, BP can be lowered to normal value. Oral drugs can be added and parenteral therapy slowly tapered off.

Hypertensive Urgency

- *Hypertensive urgency* is acute, severe elevation in blood pressure without evidence of target organ damage. Thus, the main difference between hypertensive emergency and urgency is the presence (hypertensive emergency) or absence (hypertensive urgency) of target organ damage and not the absolute value of blood pressure.
- Hypertensive urgency can be managed by oral drugs. For immediate reduction of BP in hypertensive urgency, labetalol and clonidine are useful.

Q. Define cardiomyopathy. Classify cardiomyopathies.

- Cardiomyopathies are defined as "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic."

Classification

- The traditional classification of cardiomyopathies into three categories (i.e. hypertrophic, restrictive and dilated cardiomyopathy) has many shortcomings, because, there are multiple overlaps between the etiologies and presentations of the three types. There can be mixed features and same etiology can produce different types of cardiomyopathy. The following classification is the latest one.

Table 3.48 Classification of cardiomyopathies

Type of cardiomyopathy	Examples
Primary-genetic	• Hypertrophic cardiomyopathy • Arrhythmogenic right ventricular cardiomyopathy/dysplasia
Primary-mixed (i.e. genetic and acquired)	• Dilated cardiomyopathy
Primary-acquired	• Myocarditis (inflammatory cardiomyopathy)
Secondary	• Amyloidosis • Sarcoidosis • Storage diseases (Gaucher disease, Hurler disease) • Hunter disease, hemochromatosis, glycogen storage disease, Niemann-Pick disease) • Endomyocardial fibrosis • Endocrine (diabetes, hyperthyroidism, hypothyroidism, hyperparathyroidism, pheochromocytoma, acromegaly) • Nutritional deficiencies (beriberi (thiamine); pellagra; scurvy; selenium; carnitine; kwashiorkor) • Autoimmune diseases (SLE, dermatomyositis, rheumatoid arthritis, scleroderma, polyarteritis nodosa) • Neuromuscular diseases (Friedreich ataxia, muscular dystrophy, neurofibromatosis, tuberous sclerosis) • Toxic/drugs (doxorubicin, daunorubicin, cyclophosphamide, radiation, heavy metals; chemical agents) • Postpartum

3

Q. Hypertrophic cardiomyopathy (hypertrophic obstructive cardiomyopathy (HOCM); idiopathic hypertrophic subaortic stenosis (IHSS)).

- Hypertrophic cardiomyopathy is characterized by asymmetrical ventricular hypertrophy mainly affecting interventricular (asymmetric septal hypertrophy), but in some cases the hypertrophy is localized to mid-ventricle or to the apex. The LV is usually more involved than the RV.
- There is dynamic obstruction to LV outflow during systole because the outflow tract is narrowed between the bulging septum and the anterior mitral valve leaflet. Smaller end diastolic volume increases the obstruction (sympathetic stimulation, digoxin, post-extrasystolic beat) and increased end diastolic volume decreases the obstruction.

Etiology

- It is a familial disease (autosomal dominant with variable penetrance).

Clinical Features

Symptoms

- Patients may be asymptomatic
- Family history may be present
- Dyspnea and chest pain
- Syncope occurs usually after exerscise, when diastolic filling diminishes and outflow obstruction increases.
- Arrhythmias (atrial fibrillation due to elevated LA pressure, ventricular arrhythmias)
- Sudden death often in athletes after extraordinary exertion.

Signs

- Pulsus bisferiens
- Prominent *a* wave in JVP due to reduced RV compliance.
- Triple apical impulse (due to the prominent atrial filling wave and early and late systolic impulses)
- Loud S_4
- Loud systolic murmur along the left sternal border that increases with upright posture or Valsalva's maneuver and decreases with squatting due to dynamic outflow obstruction.
- Pansystolic murmur may be present due to associated mitral regurgitation.

Investigations

- Chest X-ray is usually normal.
- ECG shows left ventricular hypertrophy and exaggerated septal Q waves.
- Echocardiogram shows asymmetric LVH, a small and hypercontractile LV. Interventricular septum is thickened. Doppler ultrasound reveals dynamic obstruction in the LV outflow tract and usually mitral regurgitation.
- Myocardial perfusion imaging may suggest septal ischemia in the presence of normal coronary arteries.
- Cardiac MRI confirms the hypertrophy.

Natural History

- It is variable.
- Malignant arrhythmias and death can happen in some patients.
- Some patients may progress to dilated cardiomyopathy.

Treatment

- Beta blockers slow the heart rate and hence increase diastolic filling time. This increases end-diastolic volume which decreases outflow obstruction. Beta blockers also reduce dyspnea, angina, and arrhythmias.
- Calcium channel blockers (especially verapamil) are also effective in symptomatic patients.
- Diuretics can be used cautiously to reduce high left ventricular diastolic pressure and pulmonary congestion.

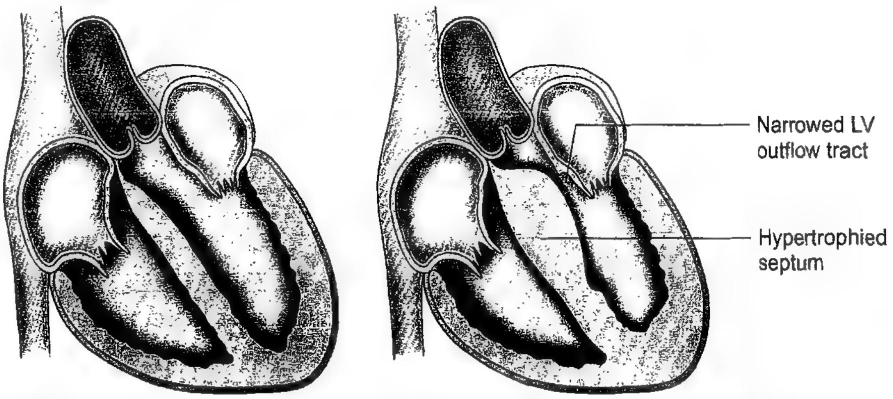


Fig. 3.8: Hypertrophic cardiomyopathy (right), left (normal)

- Treatment of arrhythmias (amiodarone, ICD implantantion).
- Nonsurgical septal ablation by injection of alcohol into septal branches of the left coronary artery in selected patients.
- Surgical resection of the outflow myocardial septum (myotomy–myomectomy) in patients with severe symptoms.

Q. Dilated Cardiomyopathy (congestive cardiomyopathy).

- Dilated cardiomyopathy (DCM) is characterized by dilation and impaired contraction of one or both ventricles.
- LV dilation and systolic dysfunction are essential for the diagnosis of dilated cardiomyopathy.

Causes of Dilated Cardiomyopathy

It can be familial or acquired. Some important causes of dilated cardiomyopathy are given below:

- Idiopathic
- Alcoholic
- Myocarditis
- Postpartum
- Nutritional (thiamine and selenium deficiency)
- Drugs (doxorubicin, cyclophosphamide)
- Endocrinopathies (thyrotoxicosis, hypothyroidism)
- Genetic diseases (hemochromatosis, glycogen storage diseases)

Clinical Features

- Clinical features are due to left and right heart failure.
- In most patients, symptoms of heart failure develop gradually.
- Symptoms are dyspnea, fatigue, peripheral edema.
- Sudden death can occur due to arrhythmias.
- Physical examination reveals signs of left heart failure such as basal lung crepitations, cardiomegaly, S_3 gallop rhythm and sometimes murmur of functional mitral regurgitation. Signs of right heart failure are elevated JVP, peripheral edema, ascites, and sometimes functional tricuspid regurgitation murmur. In severe cases, Cheyne-Stokes breathing, pulsus alternans, pallor, and cyanosis may be present.

Investigations

- *Chest X-ray*: Shows cardiomegaly, evidence for left and/or right heart failure, and pleural effusions.
- *ECG*: Sinus tachycardia, left bundle branch block and ventricular or atrial arrhythmias.
- Echocardiogram: Shows ventricular dilatation, global LV and RV systolic dysfunction. It can also exclude other diagnoses.

Treatment

- Standard therapy for heart failure (ACE inhibitor, beta-blockers, diuretics, and digoxin).
- Sodium restriction and avoidance of excessive physical activity.
- Anticoagulation to prevent thromboembolic episodes.
- Prevention and treatment of arrhythmias (anti-arrhythmics, implantable cardioverter-defibrillator (ICD)).
- Treatment of underlying cause, if any.
- Cardiac transplantation in severe cases not responding to above treatment.

Q. Restrictive cardiomyopathy (obliterative cardiomyopathy).

- Restrictive cardiomyopathy is characterized by impaired diastolic filling with normal systolic function.
- Right side of the heart is affected more commonly than left side.

Causes

- Amyloidosis (most common cause)
- Endomyocardial fibrosis
- Hemochromatosis
- Carcinoid syndrome
- Connective tissue diseases (e.g. scleroderma)
- Chemotherapy or radiation
- Hypereosinophilic syndrome
- Post-open heart surgery

Clinical Features

- It can be present at any age and is more common in women than men.
- Symptoms are due to both pulmonary and systemic congestion and include dyspnea, peripheral edema, palpitations, fatigue, weakness, and exercise intolerance.
- Pulse is either normal or of low volume with tachycardia.
- JVP is elevated with prominent y descent. An inspiratory increase in venous pressure may be seen (Kussmaul's sign).
- Congestive hepatomegaly, ascites, and peripheral edema may be present.
- The first and second heart sounds are usually normal. A third heart sound (S3 gallop) is frequently present because of the abrupt cessation of the rapid ventricular filling.

- Murmurs of functional mitral and tricuspid regurgitation may be present.

Investigations

- ECG may show non-specific ST-T changes, low voltage QRS complexes and conduction disturbances.
- Echocardiogram shows ventricular hypertrophy. Low voltage complexes in ECG but ventricular hypertrophy in ECHO is highly suggestive of restrictive cardiomyopathy.
- Cardiac MRI can show ventricular wall thickening and a distinctive pattern in amyloidosis.

Treatment

- There is no specific treatment.
- Diuretics to relieve pulmonary and systemic venous congestion.
- Digoxin may precipitate arrhythmias and should be used with caution.
- Beta blockers and calcium channel blockers help slow heart rates and improve filling.
- Excision of fibrotic endocardium (in endomyocardial fibrosis).
- Underlying cause should be treated.
- Cardiac transplantation should be performed in patients with intractable heart failure.

Q. Define myocarditis. Discuss the etiology, clinical features, investigations, and management of acute myocarditis.

- *Myocarditis* is an inflammation of the myocardium, the middle layer of the heart wall leading to cardiac dysfunction, heart failure and sudden death. It can be acute, subacute, or chronic, and there may be either focal or diffuse involvement of the myocardium.

Etiology

Table 3.49 Etiology of myocarditis

• **Infections**	*Viral:* Coxackie, influenza, HIV, dengue, parvovirus B-19, hepatitis C
	Bacterial: Acute rheumatic fever, diphtheria, tuberculosis, salmonella, brucellosis
	Protozoal: Chagas' disease, leishmaniasis
	Spirochetal: Syphilis, leptospirosis, Lyme disease
	Rickettsial: Scrub typhus, Rocky Mountain spotted fever, Q fever

(*contd.*)

Table 3.49 Etiology of myocarditis (*contd.*)

	Fungal: Candidiasis, histoplasmosis, coccidioidomycosis
	Helminthic: Trichinosis, schistosomiasis
• **Systemic disorders**	Scleroderma, sarcoidosis, SLE, Wegener's granulomatosis, giant cell myocarditis
• **Toxins and poisons**	Alcohol, arsenic, aluminium phsophide, insect bites (bee, wasp, spider, scorpion), snake bites
• **Drugs**	Anthracyclines, cyclophosphamide, antibiotics, diuretics, lithium

Clinical Features

- Myocarditis usually presents as acute congestive heart failure.
- Signs and symptoms of CCF cuch as dyspnea, orhopnea, raised JVP, peripheral edema, hypotension, S3 and S4 may be present.
- Inappropriate tachycardia.
- There may be preceding febrile illness or respiratory tract infection.
- Heart blocks can occur if the conduction system gets involved.
- If the epicardium is involved, there may be pleuritic chest pain and pericardial effusion.

Investigations

- There may be leucocytosis and raised ESR.
- CK-MB and troponins are elevated.
- Chest X-ray shows cardiomegaly. Pulmonary edema may be present.
- ECG may show nonspecific ST-T changes, conduction blocks, and ventricular ectopics.
- Echocardiography can assess the ventricular function and can exclude other diseases.
- Gallium-67 scintigraphy may reveal increased cardiac uptake in myocarditis. MRI with gadolinium enhancement reveals areas of injury throughout the myocardium.
- Endomyocardial biopsy can confirm the diagnosis, but is rarely done.

Complications

- Arrhythmias
- Heart blocks
- Congestive heart failure
- Chronic myocarditis
- Dilated cardiomyopathy.

Treatment

- Cardiac failure should be treated as per standard guidelines with ACE inhibitors, beta blockers, digoxin and diuretics.

- Patients with fulminant myocarditis require aggressive short-term support including an intra-aortic balloon pump or an LV assist device.
- Immunosuppressive agents (steroids, azathioprine) may help myocarditis of autoimmune etiology (SLE, sarcoidosis)
- Patients with severe myocarditis, without any improvement with above therapies may be eventual candidates for cardiac transplantation.

Q. What is aortic aneurysm? What are the types of aortic aneurysm?

- Aortic aneurysm is a permanent localized dilatation of the aorta having a diameter of at least 1.5 times the normal diameter of that given aortic segment.

Types

Based on the morphology, aortic aneurysm can be

- ***Fusiform***: Here the aneurysm is of uniform shape, with symmetrical dilatation that involves the full circumference of the aortic wall. This is the most common type.
- ***Saccular***: Here, the dilatation is more localized and appears as an outpouching of only a portion of the aortic wall.
- ***Pseudoaneurysm* or *false aneurysm*** refers to dilatation of only the outer layers of the vessel wall, such as occurs with a contained rupture of the aortic wall. It is not actually an aneurysm.

Q. Discuss the etiology, clinical features, investigations, complications and management of abdominal aortic aneurysm.

- Abdominal aortic aneurysm is more common than thoracic aneurysm. Abdominal aortic aneurysms is four to five times more common in men than in women.
- The infrarenal aorta is the most common site to get affected because atherosclerosis is common there.

Etiology

Table 3.30 Etiology of abdominal aortic aneurysm

• Atherosclerosis (most common cause) • Aging • Smoking • Bicuspid aortic valve and aortic coarctation • Inflammatory/infectious disorders (giant cell arteritis, syphilis, mycotic aneurysm)	• Hypertension • Genetic predisposition • Marfan syndrome • Ehlers-Danlos syndrome

Clinical Features

- Most patients are asymptomatic and are discovered incidentally on a routine physical examination or imaging study.
- Pain in the hypogastrium or lower back. Pain is steady gnawing type and may last for hours to days.
- Aneurysm expansion or impending rupture may be heralded by new or worsening pain, often of sudden onset.
- Physical examination may reveal a pulsatile mass at or above the umbilicus.
- An arterial bruit may be heard over the abdomen if there is atherosclerotic narrowing.
- When the aneurysm ruptures, patient present with abdominal pain, hypotension and a pulsatile abdominal mass.

Investigations

- X-ray abdomen may show calcified outline of aortic aneurysm.
- Ultrasound abdomen.
- CT or MR angiography.
- Conventional angiography.

Complications

- Rupture.
- DIC with hemorrhagic and thrombotic complications.

Treatment

- Risk factor reduction (stop smoking, control hypertension).
- Beta blockers reduce the rate of expansion and chances of rupture by reducing aortic pressure and the abrupt rise in pressure during systole.
- Asymptomatic—size >5.5 cm—surgical repair. Less than this—serial monitoring with ultrasound
- Symptomatic aneurysms—surgical repair irrespective of size.
- Percutaneous placement of an expandable endovascular stent graft inside the aneurysm is another new technique.
- Ruptured aneurysm—emergency surgery.

Q. Classify thoracic aortic aneurysms. Discuss the etiology, clinical features, investigations, complications and management of thoracic aortic aneurysm.

- Thoracic aortic aneurysms are less common than aneurysms of the abdominal aorta.

3

Based on Morphology

- Fusiform
- Saccular

Based on the Site of Involvement

- Aneurysm of ascending aorta
- Aneurysm of arch of aorta
- Aneurysm of descending aorta

Etiology

- See abdominal aortic aneurysm.

Clinical Features

- Can be asymptomatic.
- Pain in the chest, back, flank, or abdomen depending on the location of aneurysm.
- Symptoms due to compression or distortion of adjacent structures or vessels by ascending and arch aneurysms. These include:
  - Hoarseness of voice due to compression of left vagus or left recurrent laryngeal nerve
  - Diaphragmatic paralysis due to compression of the phrenic nerve
  - Wheezing, cough, hemoptysis, dyspnea, or pneumonitis due to compression of the tracheobronchial tree
  - Dysphagia due to compression of esophagus
  - Superior vena cava syndrome due to compression of SVC.
- Tracheal tug is descent of trachea with every heart beat. It is seen in arch of aorta aneurysm due to pulsatile pressure on the left bronchus.
- Ascending aneurysms can present with heart failure due to aortic regurgitation from aortic root dilatation and myocardial infarction due to compression of a coronary artery.
- Systemic thromboembolism due to thrombus formation within the aneurysm.

Complications

- Dissection of aneurysm.
- Rupture.

Investigations

- See abdominal aortic aneurysm.

Treatment

- See abdominal aortic aneurysm.

Q.

Aortic dissection is a life-threatening condition where the blood penetrates into the media through a tear in the intima, cleaving it into two layers longitudinally and producing a blood-filled false lumen within the aortic wall. This false lumen propagates distally (or sometimes retrograde) to a variable distance along the aorta from the site of intimal tear.

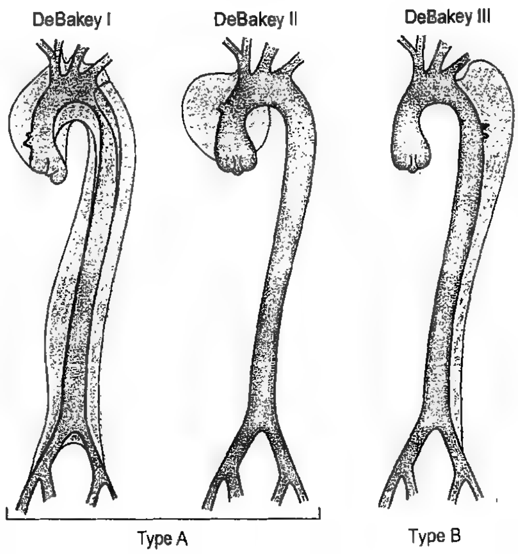
Etiology of aortic dissection

• Systemic hypertension (commonest cause)	• Bicuspid aortic valve
• Cystic medial necrosis	• Coarctation of aorta
• Preexisting aortic aneurysm	• Third trimester of pregnancy
• Vasculitis (Takayasu arteritis, giant cell arteritis, syphilis)	• Trauma
• Marfan syndrome	• High-intensity weightlifting or other strenuous exercise
• Ehlers-Danlos syndrome	• Cardiac catheterization

- *Type A*: Dissection involving the ascending aorta, regardless of the site of the primary tear
- *Type B*: Dissection of the descending aorta

DeBakey Classification

- *Type 1*: Dissection of the ascending and descending thoracic aorta
- *Type 2*: Dissection of the ascending aorta
- *Type 3*: Dissection of the descending aorta



Aortic dissection

Clinical Features

- Sudden onset severe pain in the chest, in the neck or throat, interscapular, in the lower back, or abdominal depending on the location of the aortic dissection. Pain is described as "tearing," "sharp," or "stabbing."
- There may be asymmetry of pulses.
- Hypertension is present in most patients. Rarely hypotension may be present.
- A dissection involving the ascending aorta can produce the following:
  - Acute aortic regurgitation—due to proximal aortic dissection propagating into a sinus of Valsalva with resultant aortic valve insufficiency, leading to early diastolic murmur, hypotension, or heart failure.
  - Acute myocardial ischemia or MI due to coronary occlusion.
  - Cardiac tamponade and sudden death due to rupture of the aorta into the pericardial space.
  - Neurologic deficits, including stroke or decreased consciousness due to carotid artery occlusion
  - Horner syndrome due to compression of the superior cervical sympathetic ganglion.
  - Vocal cord paralysis and hoarseness due to compression of the left recurrent laryngeal nerve.
- A dissection that involves the descending aorta can lead to splanchnic ischemia, renal failure, lower limb ischemia, or focal neurologic deficits due to spinal artery involvement and spinal cord ischemia.

Investigations

- *ECG*—shows nonspecific changes. Can rule out myocardial infarction
- *Chest X-ray*—may show widening of the aorta and mediastinum.
- *Echocardiography*—has limited utility for evaluation of the thoracic aortic dissection. Useful for proximal dissections. It is most useful for the assessment of cardiac complications of dissection, including aortic insufficiency, pericardial effusion/tamponade, and heart failure.
- *Aortography*—less commonly used now due to the availability of noninvasive imaging methods. It can identify the site of dissection, the relationship between the dissection and the major branches of the aorta, and the communication site between the true and false lumen.
- *CT angiography with three-dimensional (3D) reconstruction* is rapidly becoming the diagnostic test of choice to identify aortic dissection.
- *MRI* is as accurate as CT and is useful in patients who have contraindications to the use of intravenous (IV) contrast agents (such as renal failure or allergy).
- *Smooth muscle myosin heavy-chain assay*: Increased levels in the first 24 hours are 90% sensitive and 97% specific for aortic dissection. Levels are highest in the first 3 hours.

Treatment

- Aortic dissection is a life-threatening emergency.
- Admit the patient in ICU
- *Emergency treatment*: The goal of initial treatment is to halt any further progression of the aortic dissection and to reduce the risk of rupture. Blood pressure and the force of ventricular contraction should be reduced (systolic blood pressure to 100 to 120 mm Hg). Intravenous labetalol, which acts as an α-blocker and a β-blocker, is particularly useful in aortic dissection for controlling hypertension and contractile force. Intravenous nitroprusside should be added to if BP is not controlled with labetalol. If β-blockers are contraindicated, calcium channel blockers (diltiazem) may be useful.
- After initial medical therapy, further treatment depends on the type of dissection.
- If the dissection involves the ascending aorta, surgical repair is indicated to minimize the risk of life-threatening complications.
- If the dissection is confined to the descending aorta, medical therapy is as good as surgical therapy. However, if there is complication such as end-organ ischemia, surgery is indicated.
- Surgical therapy involves reconstruction of the aorta. Endovascular stent-grafting has been tried as an alternative to surgery in dissections involving discending aorta.

Q. What is pericarditis? How do you classify pericarditis?

- Pericarditis is inflammation of the pericardium.
- The pericardium is a protective covering for the heart. It has two layers, the outer parietal layer, and inner visceral layer. Between these two layers there is a space called pericardial sac which contains 15–50 ml of pericardial fluid. This fluid is an ultra filtrate of plasma produced by visceral layer.
- The pericardium lubricates the surface of the heart, prevents deformation and dislocation of the heart and acts as a barrier to the spread of infection. However, the absence of pericardium does not produce any obvious clinical disease.
- Pericarditis can be classified as acute (<6 weeks), subacute (6 weeks to 6 months) and chronic (>6 months).

Q. Discuss the etiology, clinical features, investigations, and management of acute pericarditis.

- This refers to acute inflammation (<6 weeks) of the pericardium. Acute pericarditis has many causes and in some cases, the cause is unknown.

Etiology of Pericarditis

- *Idiopathic*
- *Infectious conditions*: Viral (Coxsackievirus, mumps, varicella, rubella, HIV), bacterial (tuberculosis, Staphylococcus, Streptococcus, pneumococcus, Legionella, syphilis), fungal (histoplasmosis, coccidioidomycosis, Candida), and parasitic.
- *Inflammatory conditions*: Rheumatoid arthritis, SLE, scleroderma, and rheumatic fever.
- *Metabolic disorders*: Uraemia, hypothyroidism, and hypercholesterolemia.
- *Cardiovascular disorders*: Acute MI, postmyocardial infarction (Dressler's syndrome), aortic dissection, cardiovascular procedures.
- *Miscellaneous causes*: Neoplasms (primary or secondary), drugs (doxorubicin, cyclophosphamide), irradiation, and trauma.

Clinical Features

- Sharp retrosternal and left precordial pain sometimes referred to back and left shoulder. Pain is exacerbated by movement, respiration and lying down. It is typically relieved by sitting forward. The main differential diagnoses are angina and pleurisy.
- The classical clinical sign is a triphasic pericardial friction rub corresponding to atrial systole, ventricular systole, and ventricular diastole. It may also be heard as a biphasic 'to and fro' rub corresponding to systole and diastole. It is high-pitched, scratching, and grating and heard best when firm pressure with the diaphragm of the stethoscope is applied to the chest wall at the left lower sternal border at the end of expiration with the patient leaning forward.
- There is usually fever when infection is present. Features of pericardial effusion may also be present.

Investigations

- Total leucocyte count and ESR may be elevated due to infection.
- ECG shows concave-upwards (saddle shaped) ST elevation in multiple leads, which is characteristic of pericarditis. This has to be differentiated from myocardial infarction where ST elevation is convex upwards. PR segment is depressed. Low voltage QRS complexes and electrical alternans (varying axis) may be seen if there is pericardial effusion.
- Cardiac enzymes (CK-MB and troponins) are usually normal unless there is associated myocarditis.
- Chest X-ray may show widening of cardiac shadow if there is pericardial effusion.
- Echocardiogram can show pericardial effusion clearly and help detect other cardiac abnormalities.
- *Pericardiocentesis*: If pericardial effusion is present, it should be removed and analyzed for red blood cells (RBCs), WBCs, total protein level, LDH level, and adenosine deaminase activity. Gram's stain, AFB stain, culture (ordinary and Loewenstein media) and cytology should also be done.
- CT and MRI scan of the heart should be done if the cause is not clear from the above studies.

Management

- If a cause is found, it should be treated (e.g. tuberculosis, uraemia).
- Pericardial inflammation can be decreased by NSAIDs (high-dose aspirin or indometacin or ibuprofen). Steroids (prednisone, 20 to 60 mg/day) can be used in resistant situations. These anti-inflammatory drugs should be given until the patient is afebrile and asymptomatic for 1 week, followed by a gradual taper over the next few weeks.
- Some patients may have recurrent pericarditis. For recurrent pericarditis, treatment with colchicine, or pericardiectomy should be considered.

Q. Pericardial effusion and cardiac tamponade.

- Accumulation of excessive fluid in the pericardial space is called pericardial effusion.
- When large amount of fluid collects in this space, ventricular filling is compromised leading to embarrassment of the circulation. This is known as cardiac tamponade. Tamponade is a medical emergency, which can lead to pulmonary edema, shock, and death.
- The fluid is usually an exudate but blood (hemopericardium), lymph (chylopericardium) and serosanguineous fluid (TB, malignancy) can also accumulate in the space.

Etiology

- It is same as acute pericardits.

Clinical Features

- Pericardial effusion may present with symptoms similar to acute pericarditis.
- Heart sounds are faint and distant.
- Apex beat is obscured or palpable medial to the left border of cardiac dullness.

- Pericardial rub may be heard due to pericarditis in the early stages, but this becomes quieter as fluid accumulates and separates the layers of the pericardium.
- The base of the left lung may be compressed by pericardial effusion, producing an area of dullness to percussion below the angle of the left scapula (Ewart's sign).
- If there is cardiac tamponade following additional symptoms and signs may be present:
  - Dyspnea and orhopnea
  - Hypotension
  - Raised JVP with sharp rise and x descent (Friedreich's sign)
  - Kussmaul's sign (rise in JVP during inspiration)
  - Pulsus paradoxus
  - Reduced cardiac output.

Investigations

- ***Echocardiography***: This is the most useful investigation for demonstrating the effusion and looking for evidence of tamponade.
- ***ECG***: Shows low-voltage QRS complexes.
- ***Chest X-ray***: Shows large globular or pear-shaped heart with sharp outlines (water bottle appearance).
- ***CT or MRI*** is superior to echocardiogram and is especially useful in detecting loculated pericardial effusions and pericardial thickening.
- ***Pericardiocentesis***: Emergency pericardiocentesis is indicated for cardiac tamponade under echocardiographic guidance. Pericardiocentesis is also indicated when a tuberculous, malignant or purulent effusion is suspected.
- ***Pericardial biopsy***: May be needed if tuberculosis is suspected and pericardiocentesis is not diagnostic.

Treatment

- Underlying cause should be identified and treated.
- No treatment is necessary for effusion unless tamponade is present as it resolves spontaneously.
- Pericardiocentesis is indicated to relieve the pressure if there is tamponade. A flexible drainage catheter may be left in the pericardial space for several days to avoid early reaccumulation.
- Recurrent effusions (commonly due to malignancy) may require pericardial fenestration, i.e. creation of a window in the pericardium to allow the slow release of fluid into the surrounding tissues.

Q. Constrictive pericarditis.

- Here the pericardium becomes thick, fibrous and calcified, which interferes with relaxation of the heart during diastole leading to many hemodynamic consequences.
- Constrictive pericarditis should be distinguished from restrictive cardiomyopathy because the former is treatable, whereas most cases of the latter are not.

Etiology

- Tuberculosis
- Hemopericardium
- Mediastinal irradiation
- Neoplastic disease
- Bacterial infection
- Rheumatic heart disease
- Rheumatoid arthritis and SLE
- Open-heart surgery

Clinical Features

- Many clinical features are similar to cardiac tamponade.
- Ascites, dependent edema, hepatomegaly, and raised JVP develop due to reduced ventricular filling and systemic venous congestion.
- Kussmaul's sign and pulsus paradoxus may be positive.
- Pulmonary venous congestion produces dyspnoea, cough, and PND.
- Reduced ventricular filling leads to reduced cardiac output, which causes fatigue, hypotension, and reflex tachycardia.
- A 'pericardial knock' may be heard in early diastole at the lower left sternal border due to rapid ventricular filling.
- Atrial fibrillation may develop in some cases due to atrial dilatation.

Investigations

- ***Chest X-ray***: Shows a relatively small heart. There may be pericardial calcification.
- ***ECG***: Shows low-voltage QRS complexes with generalized T wave flattening or inversion.
- ***Echocardiography*** shows thickened calcified pericardium and small ventricular cavities with normal wall thickness.
- ***CT and MRI*** are useful to assess pericardial anatomy and thickness.

Treatment

- Pericardial resection is the only definitive treatment of constrictive pericarditis. This should be carried out early before severe constriction, myocardial atrophy and liver damage develops.
- In cases of tuberculous constriction, antituberculous therapy should also be given.
- Treatment of any other underlying cause.

Q. Tuberculous pericarditis.

- Tuberculous pericarditis is invariably secondary to tuberculosis elsewhere in the body. It may occur via extension of infection from the lung or tracheobronchial tree, adjacent lymph nodes, spine, or via hematogenous spread.

Clinical Features

- Low grade fever, weight loss, and night sweats.
- Symptoms and signs of pericarditis usually insidious onset.
- There may be signs and symptoms of pulmonary tuberculosis such as cough, hemoptysis, etc.
- In late stages, patients may present with findings of constrictive pericarditis.

Investigations

- *Chest X-ray* shows cardiomegaly and pleural effusions. Pericardial calcification may be seen in late stages. Evidence of concurrent pulmonary tuberculosis may be present.
- *ECG*: Low voltage QRS complexes, inverted T waves and electrical alternans may be present. *Echocardiogram* can confirm the presence of pericardial effusion, tamponade and pericardial thickening.
- *Pericardiocentesis*: Fluid is exudative in nature with low sugar and elevated ADA. Fluid should be sent for culture of tubercle bacilli and PCR.
- *Pericardial biopsy*: May show the presence of granulomas and tubercle bacilli.
- *Montoux test*: Most patients will have positive skin test. A negative test suggests low probability of pericardial tuberculosis.

Treatment

- Antituberculous therapy for 6 to 9 months. Four drugs should be given for initial 2 months (isoniazid, rifampicin, pyrazinamide, ethambutol) followed by 2 drugs (isoniazid and rifampicin) for 4 to 7 months.
- Steroids along with antituberculous drugs reduce mortality, the need for subsequent pericardiocentesis and the chances of constrictive pericarditis.
- Therapeutic aspiration may be needed to relieve symptomatic effusion or tamponade.
- If constrictive pericarditis develops, pericardiectomy may be needed.

4 Diseases of Gastrointestinal System

Q. Define the terms nausea, vomiting, retching, regurgitation, rumination and indigestion.

- ***Nausea*** is the subjective feeling of need to vomit. It precedes vomiting and may happen alone, without retching or vomiting.
- ***Vomiting*** (or *emesis*) is the forceful ejection of upper gastrointestinal contents through the mouth resulting from contractions of gut and thoracoabdominal wall musculature.
- ***Retching*** is voluntary muscle activity of the abdomen and thorax without discharge of gastric contents through the mouth.
- ***Regurgitation*** is effortless return of gastric or esophageal contents into the mouth without nausea. It occurs without abdominal, thoracic, or gastrointestinal muscle contractions.
- ***Rumination*** (merycism) is effortless but purposeful regurgitation of food from the stomach into the mouth, where it is rechewed and reswallowed.
- ***Indigestion*** is a nonspecific term that encompasses a variety of upper abdominal complaints including nausea, vomiting, heartburn, regurgitation, and dyspepsia (upper abdominal discomfort or pain).

Q. Discuss the causes and mechanism of vomiting. How do you approach and manage a case of vomiting?

- *Vomiting* (or *emesis*) is the forceful ejection of upper gastrointestinal contents through the mouth resulting from contractions of gut and thoracoabdominal wall musculature.
- In projectile vomiting, vomiting is not preceded by nausea.
- Most common causes of nausea and vomiting are acute gastroenteritis, systemic febrile illnesses and medications.

Table 4.1 Causes of vomiting

Causes	Examples
Gastrointestinal diseases	Gastritis, cholecystitis, appendicitis, gastroenteritis, intestinal obstruction, peptic ulcer, pancreatitis, peritonitis
Drugs and toxins	Digoxin, levodopa, opiates, anticancer drugs, alcohol excess
Acute infections	Hepatitis, influenza, malaria, urinary tract infection
CNS diseases	Raised intracranial pressure, meningitis, migraine
Reflex	In intense pain (myocardial infarction, ureteric stone)
Psychogenic	Unpleasant taste or smell, psychogenic stress, seeing fearful scenes
Labyrinthine disorders	Motion sickness, space sickness, viral labyrinthitis, acoustic tumors, and Ménière's disease
Metabolic causes	Uraemia, diabetic ketoacidosis, hypercalcaemia, Addisons disease
Pregnancy	
Postoperative	

Mechanism of Vomiting

- Vomiting is coordinated by the brainstem and is effected by neuromuscular responses in the gut, pharynx, and thoracoabdominal wall. There are three phases of vomiting; nausea, retching and actual act of vomiting.
- There is no single vomiting centre as believed earlier. There are many nuclei in the lateral reticular formation of the medulla which are stimulated by the chemoreceptor trigger zones (CTZs) in the floor of the fourth ventricle, and also by vagal afferents from the gut. Many causes of vomiting act through stimulation of CTZs or vagal afferents. Several other brainstem nuclei integrate the responses of the gastrointestinal, respiratory, pharyngeal, and abdominal muscles during the act of vomiting.

- During vomiting, thoracic and abdominal muscles contract, producing high intrathoracic and intra-abdominal pressures which expel the gastric contents. The gastric cardia herniates through the diaphragm, there is intense salivation and the larynx moves upward to promote oral propulsion of the vomitus. There is reversal of peristaltic waves which assist in the oral expulsion of small-intestinal contents.

Approach to a Case of Vomiting

History

- ***Duration***: Acute vomiting refers to vomiting of ≤1 week. Causes of acute vomiting include obstruction, ischemic, toxic, metabolic, infectious, neurological and post-operative reasons. Chronic vomiting refers to vomiting lasting more than 1 month. Causes of chronic vomiting include partial intestinal obstruction, motility disorder, chronic neurological conditions (such as chronic meningitis, brain tumor), pregnancy or functional reasons.
- ***Time of onset***: Acute onset—gastroenteritis, pancreatitis, cholycystitis, appendicitis, anaphylaxis, medication effect. Early morning vomiting seen in raised intracranial tension, pregnancy, and uremia. Vomiting 1 hour after eating suggests gastric outlet obstruction or gastroparisis. Vomiting few hours after eating suggests gastric or intestinal obstruction.
- ***Content of the vomitus***: If bilious then gastric outlet obstruction can be ruled out, otherwise bile from duodenum cannot come back to stomach. Undigested food suggests achalasia or stricture. If hematemesis suspect upper GI bleed with its causes. If fecal mater present suspect distal bowel obstruction.
- ***Associated symptoms***: Chronic headaches associated with vomiting is seen in intracranial lesion and migraine. Vomiting without preceding nausea (projectile vomiting) is typical of central nervous system pathology. Vertigo suggests a labyrinthine or vestibular problem. Associated diarrhea suggests gastroenteritis. Fever suggests an infection. Severe colicky abdominal pain suggests biliary, ureteric or intestinal obstruction.
- ***Past medical and surgical history***: The past medical history will reveal the presence of any GI disease or previous surgeries.

Physical Examination

- Assessment of the patient's hydration status and vital signs. Tachycardia and hypotension may be present if there is hypovolemia. Fever can be present in infections.
- Abdomen should be examined for any abnormality such as distension (seen in intestinal obstruction, peritonitis), tenderness, guarding (seen in abdominal infections), bowel sounds (increased in intestinal obstruction and decreased in peritonitis and paralytic ileus).
- Other systems should be examined for any abnormality.

Investigations

- ***CBC***: If Hb and hematocrit are high, it indicates dehydration. Leukocytosis is seen in infections.
- ***Serum electrolytes***: To rule out hypochloremia, hypokalemia, etc.
- ***Urea, creatinine***: Renal failure can cause vomiting due to uremia. On the other hand vomiting itself can cause renal failure if there is dehydration.
- ***Serum amylase, lipase***: Elevated in pancreatitis.
- ***Liver function tests***: To rule out hepatitis.
- ***Erect abdomen X-ray***: If any intra-abdominal pathology suspected. Dilated bowel loops with multiple air fluid level seen in peritonitis and intestinal obstruction.
- ***Ultrasound abdomen***: To rule out any intra-abdominal pathology.
- ***Upper GI endoscopy***: If peptic ulcer or gastric outlet obstruction is suspected or if hematemesis is present.
- ***CT abdomen***: If the cause of vomiting is not clear from above investigations.
- Other tests as indicated.

Complications of Vomiting

- ***Aspiration***: Vomiting in a patient with altered mental status, low or depressed level of consciousness, or persistent vomiting can lead aspiration of vomitus to the lungs and cause asphyxia or aspiration pneumonia.
- ***Mallory Weiss syndrome***: Due to severe and repetitive retching and vomiting a partial tear of the mucosa and sub-mucosa in the stomach and gastroesophageal junction can occur and lead to bleeding and hematemesis.
- ***Boerhaave syndrome***: This is a full thickness tear of all the layers of the esophagus, commonly in the lower part of the esophagus due to repetitive, bouts of retching and vomiting. It is a medical emergency.
- ***Hypovolemia***: Recurrent vomiting can cause dehydration and hypovolemia due to loss of water content.
- ***Electrolyte imbalance***: Hypokalemia occurs due to hypovolemia which stimulates renin angiotensin aldosterone system (RAAS) leading to sodium absorption and potassium excretion in the urine.
- ***Hypochloremic metabolic alkalosis***: This occurs due to loss of H^+ and chloride which are present in the gastric juice in the vomitus.

Treatment of Vomiting

- Underlying cause should be treated
- In severe persistent vomiting, patient should be kept NPO and IV fluids administered.
- Antiemetics can be used for symptomatic control of vomiting. Examples: Domperidone 10 mg TID, metoclopramide 10 mg TID, ondansetron 4 mg TID.

Q. Causes of loss of appetite.

Infections: Viral fever, tuberculosis or any other infection
Gastrointestinal diseases: Peptic ulcer, pancreatitis
Liver diseases: Hepatitis, cirrhosis
Renal disease: Renal failure
Endocrine causes: Hypothyroidism, Addison's disease, hyperparathyroidism
Malignancies: Carcinoma stomach, pancreas or any other malignancy, leukemias, lymphomas
Psychiatric disorders: Depression, anorexia nervosa

Q. Define diarrhea, pseudo-diarrhea and fecal incontinence.

Q. What are the causes of acute diarrhea? How do you evaluate and manage a case of acute diarrhea?

- Diarrhea is defined as abnormal increase in stool liquidity, frequency and quantity. Typically a stool weight >200 g/d or frequency more than 3 times per day is considered to indicate diarrhea.
- Depending on the duration, diarrhea may be classified as acute if <2 weeks, persistent if 2 to 4 weeks, and chronic if >4 weeks in duration.
- Diarrhea should be differentiated from pseudodiarrhea, and fecal incontinence. Pseudodiarrhea is frequent passage of small volumes of stool. It is seen in irritable bowel syndrome and anorectal disorders such as proctitis. Fecal incontinence is involuntary discharge of fecal matter and is seen in neuromuscular disorders and structural anorectal problems.

Causes of Acute Diarrhea

Table 4.2 Causes of acute diarrhea

Bacterial

Preformed enterotoxin production
- *Staphylococcus aureus*
- *Bacillus cereus*
- *Clostridium perfringens*

Enterotoxin production
- Enterotoxigenic *E. coli* (ETEC)
- *Vibrio cholerae*

Cytotoxin production
- Enterohemorrhagic *E. coli* O157:H5
- *Vibrio parahaemolyticus*
- *Clostridium difficile*

Mucosal invasion
- Shigella
- Salmonella
- *Campylobacter jejuni*
- Enteroinvasive *E. coli* (EIEC)
- *Yersinia enterocolitica*
- Chlamydia
- *Neisseria gonorrhoeae*
- *Listeria monocytogenes*

Viral
- Noroviruses
- Rotavirus
- Cytomegalovirus

Protozoal
- *Giardia lamblia*
- Cryptosporidium
- Cyclospora
- *Entamoeba histolytica*

Pathophysiology of Diarrhea

- Diarrhea is the reversal of the normal net absorptive status of water and electrolyte absorption to secretion. Such a derangement can be the result of either an osmotic force that acts in the lumen to drive water into the gut (osmotic diarrhea) or the result of an active secretory state induced in the enterocytes (secretory diarrhea).
- Example of osmotic diarrhea is lactulose induced diarrhea. In secretory diarrhea, the epithelial cells' ion transport processes are turned into a state of active secretion. Example of secretory diarrhea is bacterial infection of the intestine. Pathogens can induce secretary diarrhea through multiple mechanisms such as production of enterotoxins or cytotoxins, release of cytokines, etc.

Evaluation of a Patient with Acute Diarrhea

History

- Residence.
- Occupational exposure.
- Recent and remote travel (suspect diseases endemic in the area of travel).
- Duration of diarrhea (whether acute or chronic, because the causes are different).
- Frequency and quantity of stools (to assess the severity of diarrhea).
- *Appearance of stools*: Rice water stool is seen in cholera, pea soup appearance in enteric fever, brown coloured in amebiasis.

- Presence of blood and/or mucus (suggests invasive infection. Fresh blood and mucus is seen in large intestinal diarrhea).
- Any associated vomiting (suggests food poisoning or gastroenteritis).
- H/o pain abdomen (suggests invasive infection).
- Urine output (to assess dehydration).
- H/o fever (suggests infection with invasive organisms).
- Food history can give clue about food poisoning and possible pathogen.
- Recent antibiotic use (may suggest antibiotic induced diarrhea due to *C. difficile*).
- H/o immunocompromised state (suspect diarrhea due to unusual organisms such as cryptosporidia, isospora belli, etc).
- *H/o animal exposure*: Exposure to young dogs or cats is associated with *Campylobacter* organisms. Exposure to turtles is associated with *Salmonella* organisms.

Examination

- Look for any signs of dehydration. Assess pulse, BP, postural hypotension, skin turgor, dryness of mucus membranes.
- Assess conscious level as patient can be in altered sensorium due to electrolyte imbalance.
- Examine the abdomen for any distension, tenderness and bowel sounds.

Investigations in Acute Diarrhea

- Most cases of acute diarrhea improve spontaneously with supportive treatment and do not require investigations. However, acute diarrhea should be investigated if it is severe with dehydration, associated with bloody stools, fever, lasts more than 2 days without improvement, new community outbreaks, severe abdominal pain and in immunocompromised patients.

Complete Blood Count (CBC)

- Hemoconcentration and leucocytosis is commonly seen. High leucocyte count suggests infectious diarrhea.

Urea/Creatinine, Serum Electrolytes

- Urea and creatinine may be elevated due to prerenal azotemia. Electrolyte disturbances such as hyponatremia and hypokalemia occur in severe diarrhea.

Stool Analysis

- Stool should be sent for bacterial and viral cultures, microscopy for ova and parasites, immunoassays for bacterial toxins (*C. difficile*), viral antigens (rotavirus), and protozoal antigens (Giardia, *E. histolytica*). Pathogens can also be identified by detecting their DNA sequences.

Ultrasound Abdomen

- Useful if there is severe abdominal pain or abdominal distension or any mass is felt.

GI Scopy

- If stool analysis does not reveal the cause of diarrhea, then flexible sigmoidoscopy with biopsies and upper endoscopy with duodenal aspirates and biopsies may be indicated.
- Colonoscopy may be indicated to identify any growth, or to exclude inflammatory bowel disease.

CT Scan Abdomen

- Is useful in the evaluation of ischemic colitis, diverticulitis, or partial bowel obstruction

Assessment of Dehydration

Table 4.3 Assessment of dehydration

Feature	Mild dehydration	Moderate dehydration	Severe dehydration
General	Well	Restless	Lethargic
Oral mucosa	moist	Dry	Very dry
Skin	Normal	Cool	Cool
Skin turgor	Normal	Reduced	Markedly reduced
Capillary refilling	Normal	Slow	Very slow
Eyes	Normal	Sunken	Markedly sunken
Pulse rate	Normal	Tachycardia	Markedly increased
JVP	Normal	Collapsed	Collapsed
BP	Normal	Postural drop or reduced	Hypotension/ shock
Respiration	Normal	Normal	Increased
Urine output	Normal	Reduced	Markedly reduced
Urine specific gravity	<1.020	>1.020	>1.035
Blood urea	Normal	Normal or high	High

Treatment

Fluid and Electrolyte Replacement

- This is very important in acute diarrhea since dehydration is the major cause of death. If the patient is able to take orally, oral fluid replacement (ORS) can be given in mild to moderate dehydration. Intravenous rehydration is required if the patient is not able to take orally, in severe dehydration, in infants, and elderly.

Antimotility Agents

- Agents like loperamide, diphenoxylate/atropine combination decrease the frequency and quantity of diarrhea. They can be used in diarrhea without fever and without blood in stools. These agents should be avoided in infective diarrhea (febrile dysentery), which may be exacerbated or prolonged by them.

Antisecretory Agents

- Example is racecadotril
- Inhibits secretion of water and electrolytes into the intestinal lumen.
- Acts by inhibiting encephalinase.
- Dose is 100 mg TID.
- It is useful in acute watery diarrhea.
- It is contraindicated in renal failure, pregnancy and breastfeeding.

Antispasmodics

- Such as dicyclomine, hyoscine, etc. can be used in patients with crampy abdominal pain.

Antibiotics

- Moderately to severely ill patients with febrile dysentery may be empirically treated with a quinolone, such as ciprofloxacin (500 mg bid for 3 to 5 d).
- Empirical treatment with metronidazole can also be given for suspected giardiasis or amebiasis (400 mg TID for 5–7 d).
- Antibiotic therapy may be modified when specific pathogen is identified.
- Antibiotics should also be given to patients who are immunocompromised, have mechanical heart valves or recent vascular grafts, or are elderly even if the organism is not identified.

Q. Traveler's diarrhea.

- Traveler's diarrhea refers to diarrhea occurring in persons traveling from resource-rich to resource-poor regions of the world. It is common among travelers to developing countries.
- Food and water contaminated with fecal matter are the main sources of infection. Bacteria such as enterotoxigenic *Escherichia coli*, enteroaggregative *E. coli*, Campylobacter, Salmonella, and Shigella are common causes of traveler's diarrhea.
- Most cases are benign and self-limited, but occasionally can be severe enough to cause dehydration and other complications.

Causes

Table 4.4 Causes of traveler's diarrhea

Bacteria	Viruses
• Enterotoxigenic *Escherichia coli* • *Campylobacter jejuni* • Salmonella • Shigella • *Vibrio parahaemolyticus* • *Vibrio cholerae* • *Yersinia enterocolitica*	• Rotavirus • Norwalk virus **Parasites** • *Giardia lamblia* • Entamoeba histolytica

- These organisms are often transmitted by food and water.
- More than 90 percent cases are due to bacteria; the most common being enterotoxigenic *Escherichia* coli (ETEC).

Clinical Features

- Most cases occur withing first 2 weeks of travel.
- Abdominal cramps followed by sudden onset, watery diarrhoea, lasting 2–5 days.
- Malaise, anorexia, nausea, vomiting, and fever.
- Diffuse tenderness over abdomen.
- Additional specific features may be present depending on the organism.

Treatment

- ***Fluid replacement*:** Most cases are self-limited and resolve on their own within three to five days of treatment with fluid replacement only. Oral fluid replacement is enough in most cases. Broth, fruit juice, or similar fluids may be used. ORS is especially useful in severe diarrhea.
- ***Antibiotics*:** Shorten the disease duration to about one day. Antibiotics are indicated in patients with severe diarrhea associated with fever, blood, pus or mucus in the stool. Ciprofloxacin or norfloxacin may be used. Bismuth subsalicylate can also be used.
- ***Antimotility agents*:** Antimotility agents such as loperamide (Imodium) or diphenoxylate (Lomotil) can be used to reduce severity of diarrhea. However, caution should be exercised in using these agents in bloody diarrhea.

Prevention

- ***Improving food and drink selection*:** Avoid raw food items such as chutney, salads, buttermilk, and curds. Use only boiled or bottled water. Avoid fresh fruit juices with ice.
- ***Prophylactic antibiotics*:** Not routinely necessary. Quinolones or doxycycline 100 mg/day for a few weeks. Bismuth subsalicylate 60 ml four times a day is an alternative. Rifaximin may prove to be the preferred antibiotic because it is not absorbed and is well tolerated.

- *Probiotics*: Such as *Lactobacillus* and *Saccharomyces boulardii* have been shown to decrease the incidence of diarrhea in travelers.

Q. Define chronic diarrhea. What are the causes of chronic diarrhea? How do you investigate and manage a case of chronic diarrhea?

- Chronic diarrhea is defined as diarrhea lasting for more than 4 weeks.

Causes of Chronic Diarrhea

Table 4.5 Causes of chronic diarrhea

Osmotic diarrhea
- Intake of lactulose, sorbitol
- *Disaccharidase deficiency*: Lactose intolerance

Secretory diarrhea
- *Hormonally mediated:* VIPoma, carcinoid, medullary carcinoma of thyroid (calcitonin), Zollinger-Ellison syndrome (gastrin)
- *Laxatives;* phenolphthalein, senna
- *Villous adenoma*
- *Bile salt malabsorption* (ileal resection; Crohn's ileitis; post-cholecystectomy)

Inflammatory conditions
- Inflammatory bowel disease (ulcerative colitis and Crohn's disease)
- Radiation enteritis

Malabsorption syndromes
- Celiac sprue, tropical sprue, Whipple's disease, eosinophilic gastroenteritis, small bowel resection (short bowel syndrome), chronic pancreatitis

Motility disorders
- *Postsurgical*: Vagotomy, partial gastrectomy
- Blind loop with bacterial overgrowth
- Scleroderma
- Diabetes mellitus
- Hyperthyroidism
- Irritable bowel syndrome

Chronic infections
- *Parasites*: *Giardia lamblia*, *Entamoeba histolytica*
- Intestinal tuberculosis
- *AIDS related infections*: *Mycobacterium avium* complex, microsporida, cryptosporidium, *Isospora belli*

Factitious
- Intake of antacids and laxatives, bulimia

Malignancy
- Lymphoma of intestine, adenocarcinoma colon

Investigations in Chronic Diarrhea

- In contrast to acute diarrhea, most cases of chronic diarrhea are noninfectious.
- All the tests described for acute diarrhea are required for chronic diarrhea.
- 24-hour stool fat estimation, testing for presence of laxatives, and estimation of stool osmolality (normal osmotic gap in secretory diarrhea, increased in osmotic diarrhea) should be done.
- Intestinal aspirates and quantitative cultures to rule out small bowel bacterial overgrowth.
- If suggested by history or other findings, hormonal excesses should be ruled out by appropriate tests (serum gastrin, VIP, calcitonin, thyroid function tests, etc).
- Low fecal pH suggests carbohydrate malabsorption; lactose malabsorption can be confirmed by lactose breath testing or by a therapeutic trial with lactose exclusion and observation of the effect of lactose challenge.
- Pancreatic disease should be excluded by secretin-cholecystokinin stimulation test, or by assay of fecal chymotrypsin activity or a bentiromide test.
- Ultrasound abdomen to rule out pancreatitis, malignancy, and pancreatitis.
- Colonoscopy to rule out ileocecal TB, Ca colon, inflammatory bowel disease, etc.
- CT abdomen if malignancy or pancreatitis or abdominal TB is suspected.

Treatment of Chronic Diarrhea

- Treatment of chronic diarrhea depends on the specific etiology. For example, elimination of lactose containing foods in lactase deficiency or gluten in celiac sprue, use of steroids or anti-inflammatory agents in inflammatory bowel diseases, psychiatric treatment in factitious diarrhea, etc.

Q. Define constMipation. Enumerate the causes of constipation. How do you investigate and treat a case of constipation?

- Constipation may be defined as infrequent stools (less than 3 times in a week), hard stools, excessive straining, or a sense of incomplete evacuation.
- Risk factors for constipation include female sex, older age, inactivity, low caloric intake, low fiber diet, and taking a large number of medications. The incidence of constipation is three times higher in women.

Causes of Constipation in Adults

Table 4.6 Causes of constipation in adults

• ***Common causes***	Inadequate fiber or fluid intake, sedentary lifestyle, irregular bowel habits
• ***GI diseases***	Intestinal obstruction, colonic neoplasm, colonic stricture, anal fissure, painful hemorrhoids, anal sphincter spasm, pelvic floor dysfunction, descending perineum syndrome, rectal mucosal prolapse, rectocele, Hirschsprung's disease, Chagas' disease, irritable bowel syndrome
• ***Endocrinopathies***	Hypothyroidism, hyperparathyroidism, hypercalcemia, diabetes mellitus
• ***Psychiatric disorders***	Depression, eating disorders
• ***Neurologic diseases***	Parkinsonism, multiple sclerosis, spinal cord injury, paraplegia, autonomic neuropathy
• ***Myopathic diseases***	Systemic sclerosis, myotonic dystrophy
• ***Metabolic***	Hypokalemia, hypercalcemia, uremia, porphyria
• ***Drugs***	Ca^{2+} channel blockers, antidepressants, opioids, anticholinergics, clonidine, calcium and iron supplements

Approach to a Case of Constipation

History

- Confirm what exactly the patient means and whether there is really constipation. A constipated patient may be otherwise totally asymptomatic or may complain of one or more of the following: straining, lumpy or hard stools, sensation of anorectal obstruction, sensation of incomplete defecation, manual maneuvering required to defecate, abdominal bloating, pain on defecation, and rectal bleeding.
- Ask about the frequency of stools, consistency (lumpy/hard), excessive straining, or prolonged defecation time.
- Presence of blood in the stool and weight loss should be taken seriously as it can indicate carcinoma colon. Similarly presence of vomiting, inability to pass flatus and pain abdomen indicates intestinal obstruction.
- Ask about the symptoms of any underlying disease (see the causes above).
- Ask about food habits, activity, and drug intake.

Examination

- Do a complete physical examination and rectal examination.
- Look for any hernias which can cause constipation or the result of chronic constipation.
- Look for any mass in the abdomen.
- Look for any evidence of endocrine (hypothyroidism) or neurological abnormalities.

Investigations

- Based on the history and examination findings investigations are ordered as follows:

Blood tests

- Serum calcium, blood sugar, thyroid and parathyroid function tests, if clinically indicated.

Stool examination

- Look for occult blood (presence of blood may suggest Ca colon)

Sigmoidoscopy, barium enema, colonoscopy

- These are indicated to rule out local anorectal abnormalities. Colonoscopy is especially important in patients above 40 years with history of weight loss, rectal bleeding, or anemia to rule out colonic cancer.

Colon transit time

- This is measured by performing an abdominal radiograph 120 hours after ingestion of radiopaque markers. Retention of >20% of the marker indicates prolonged transit.

Balloon expulsion testing, anal manometry, and defecograph

- These tests can be used to assess pelvic floor dysfunction and anorectal disorders.

Treatment

- ***General measures***: Increase fluid intake, high fiber diet and physical activity.
- ***Bulk laxatives***: These include psyllium (ispaghula), methylcellulose, and calcium polycarbophil. They exert their laxative effect by absorbing water and increasing fecal mass. They are well tolerated. They may be used alone or in combination with dietary changes. Side effects are impaction above strictures, gas and bloating.
- ***Emollients (stool softeners)***: Include docusate sodium and liquid paraffin. Docusate sodium acts by lowering the surface tension of stool, thereby allowing water to easily enter the stool. Liquid paraffin works by lubricating the stool. They are generally inferior to bulk laxatives, but more useful in patients with anal fissures

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and hemorrhoids which cause painful defecation. They are generally well tolerated. Liquid paraffin can cause depletion of fat soluble vitamins if used for long time.

- ***Osmotic laxatives***: Include magnesium sulfate, lactulose, polyethylene glycol, sorbitol, and glycerine. These agents are poorly absorbed and act as hyperosmolar solutions which retain water in the intestinal lumen. Magnesium sulfate can cause hypermagnesemia in patients with renal failure. Other agents can cause flatulence and abdominal bloating.
- ***Stimulant laxatives***: These include castor oil, bisacodyl and senna. They increase intestinal motility and secretion of water into the bowel. They can cause electrolyte imbalance such as hypokalemia.
- ***Prokinetic agents***: Metoclopramide and mosapride. They increase intestinal motility.
- ***Enemas***: Enemas act within 5–15 min and are given rectally. These include tap water enema, soap water enema, sodium phosphate enema, etc. Rarely if stools are impacted, digital evacuaton has to be done.
- ***New agents***: Newer therapies for constipation include prucalopride, a prokinetic agent that stimulates colonic motility and decreases transit time, and the osmotic agents lubiprostone and linaclotide, which stimulate intestinal fluid secretion by acting on the intestinal mucosa. Lubiprostone and linaclotide are useful in chronic idiopathic constipation and constipation caused by irritable bowel syndrome. Naloxegol and methylnaltrexone are useful in opioid induced constipation.

Q. Enumerate the causes of occult blood in the stool.

- Occult bleeding refers to positive fecal occult blood test without visible fecal blood either to the patient or physician.

Causes

Table 4.7 Causes of occult blood in the stool

Upper GI lesions	Lower GI lesions
• Esophagitis • Peptic ulcer disease • Gastritis/erosions • Duodenitis/erosions • Angiodysplasia • Esophageal or gastric varices • Gastric cancer • Gastric or duodenal polyps	• Colon polyps • Colon cancer • Angiodysplasia • Colonic ulcers • Hemorrhoids • Anal fissure **Hookworm infestation** **Drugs:** Aspirin or other NSAIDs

Q. Enumerate the causes of weight loss.

Table 4.8 Causes of weight loss

Involuntary weight loss	Voluntary weight loss
• Endocrine disorders (hyperthyroidism, pheochromocytoma, adrenal insufficiency) • Uncontrolled diabetes mellitus • Malignancy • Chronic infections (tuberculosis, HIV, subacute bacterial endocarditis) • GI disorders (malabsorption syndromes, chronic pancreatitis, IBD, parasitic infestation) • COPD • Chronic renal failure • Psychiatric disorders (depression, mania, anorexia nervosa, schizophrenia) • Chronic alcoholism • Drugs (opiates, amphetamines, digoxin, metformin, NSAIDs, anticancer drugs)	• Treatment of obesity • Anorexic drugs—amphetamines and derivatives • Distance runners, models, ballet dancers, gymnasts • Marked increase in physical activity • Prolonged fasting

Q. Aphthous ulcers.

- These are painful oral ulcers which are localized, shallow, round to oval, with a grayish base.
- Apthous ulcers are common in childhood and adolescence and become less frequent in adulthood. They usually heal within 10 to 14 days without scarring.

Etiology

- Exact cause of aphthous ulcers is not well known. Alterations in local cell mediated immunity may play a role in the causation.
- A genetic basis exists for some recurrent apthous ulcerations. This is shown by a positive family history in about one third of patients with recurrent apthous ulcerations.
- Recurrent apthous ulcers are seen in stress, infections, food allergy, HIV infection, celiac sprue, gluten sensitive enteropathies, inflammatory bowel diseases, Behçet's disease and vitamin and mineral deficiencies (B vitamins, iron, folic acid, and zinc). Drugs like methotrexate may induce oral ulcers.

Treatment

- Local corticosteroid application (triamcinolone gel and hydrocortisone pellets) and other topical analgesics are adequate. These are applied to the ulcer two to four times daily until the ulcer is healed.

- Chlorhexidine gluconate mouth rinses reduce the severity and pain of ulceration but not the frequency.
- Oral corticosteroids are indicated for severe disease.
- Colchicine, dapsone, pentoxifylline, interferon alpha, and levamisole are beneficial in severe recurrent apthous ulcers.
- Thalidomide is useful for severe recurrent apthous ulcers especially in patients with HIV infection.

Q. What is hiatus hernia? Discuss the causes, clinical features, diagnosis and management of hiatus hernia.

Q. Sliding hiatus hernia

Q. Para-esophageal or rolling hernia.

- Hiatus hernia is herniation of a part of the stomach into the thoracic cavity through the esophageal hiatus of the diaphragm. There are two types: (1) *sliding hiatus hernia* and (2) *para-esophageal or rolling hernia.*

Sliding Hiatus Hernia

- Here, the gastroesophageal junction and fundus of the stomach slide upward through the hiatus and lie above the diaphragm.

Etiology

- Incidence increases with increasing age.
- Weakening of the anchors of the gastroesophageal junction to the diaphragm and longitudinal contraction of the esophagus.
- Increased intra-abdominal pressure (ascites, pregnancy, obesity).
- Trauma.
- Congenital malformation.

Clinical Features

- It does not produce symptoms on its own; symptoms occur because of associated gastroesophageal reflux.
- Symptoms are epigastric or substernal pain, postprandial fullness, nausea, and retching.

Investigations

- Chest X-ray: May show retrocardiac air fluid level or intrathoracic stomach.
- Barium swallow will demonstrate the presence of gastroesopahgeal junction in the thorax.
- Endoscopy.

Management

- Asymptomatic sliding hiatus hernia does not require any treatment.
- Symptomatic large hiatus hernia requires either medical or surgical treatment. Surgical treatment involves repair of the diaphragmatic defect, and fixing the stomach in the abdominal cavity (fundoplication) combined with an anti-reflux procedure.

Para-esophageal or Rolling Hernia

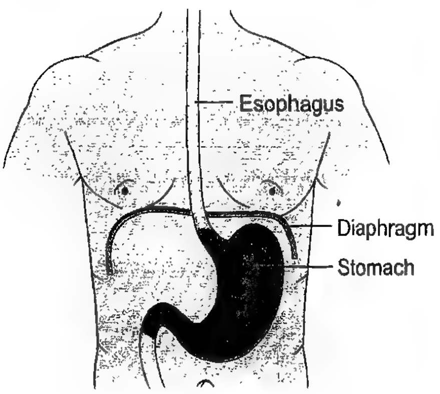
- Here, the gastroesophageal junction remains fixed in its normal location but a small part of the fundus of the stomach rolls up through the hiatus alongside the oesophagus.

Etiology

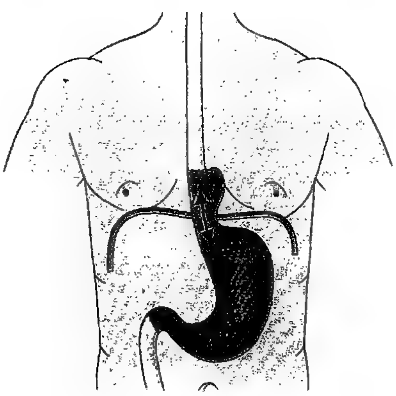
- Unknown
- Post-surgical (e.g. after antireflux procedures, esophagomyotomy, or partial gastrectomy).

Clinical Features

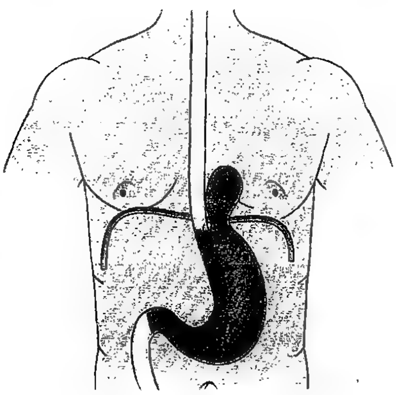
- Clinical features are same as sliding hiatus hernia.



Normal esophagus and stomach



Sliding hiatus hernia



Paraesophageal hiatus hernia

Fig. 4.1

- Complications are common in this variety and include dysphagia, gastritis, ulceration, volvulus and strangulation. Respiratory complications can occur due to compression of the lung by the herniated viscera.

Investigations

- Same as sliding hiatus hernia.

Treatment

- Involves, reduction of the herniated stomach into the abdomen, herniotomy, herniorraphy combined with an antireflux procedure and gastropexy (attachment of the stomach sub-diaphragmatically to prevent reherniation)

Q. What is gastroesophageal reflux disease (GERD)? Describe the etiology, pathophysiology, clinical features, investigations, complications and treatment of reflux esophagitis.

- Gastroesophageal reflux is the movement of gastric contents into the esophagus. It occurs in everyone, multiple times every day.
- It becomes pathological, when the antireflux mechanisms fail sufficiently to allow gastric contents to make prolonged contact with the lower esophageal mucosa causing damage (GERD). Reflux esophagitis is the commonest form of GERD, most often recognized by recurrent heartburn.

Etiology of GERD

- Pregnancy, obesity, ascites and weight lifting act by increasing intra-abdominal pressure.
- Fat, chocolate, smoking, coffee, large fatty meals or alcohol ingestion reduce lower esophageal sphincter tone.
- *Drugs*: Calcium-channel blockers, nitrates reduce sphincter tone.
- Systemic sclerosis reduces sphincter tone and esophageal motility.
- After treatment for achalasia-reflux increases.
- Sliding hiatus hernia predisposes to reflux because the gastroesophageal junction lies above the diaphragm and hence the sphincter effect of diaphragm is lost.

Pathophysiology

- Esophagus is a 25 cm conduit whose upper third is skeletal muscle and lower two-thirds is smooth muscle. There is a sphincter in the lower esophagus (LES) formed by the lower 4 cm of esophageal smooth muscle. It relaxes after swallowing to allow food to enter the stomach and closes after swallowing thereby preventing reflux. Sphincter tone can increase in response to rises in intra-abdominal and intragastric pressures. Reflux is also prevented by contraction of the crural diaphragm which surrounds lower end of esophagus and exerts a 'pinchcock-like' action at the LES.
- When these mechanisms fail, abnormal acid reflux occurs and damages the lower end of esophagus. Damage to esophagus produces mild esophagitis (mild erythema) and erosive esophagitis (mucosal damage, bleeding, superficial linear ulcers, and exudates). Erosive esophagitis may heal by intestinal metaplasia (Barrett's esophagus), which is a risk factor for adenocarcinoma.

Clinical Features

- Regurgitation of sour material in the mouth and heartburn are the main features of GERD. Angina like pain can occur in some patients. Heartburn is due to contact of refluxed material with the sensitized or ulcerated esophageal mucosa. The correlation between heartburn and esophagitis is poor. Patients with severe esophagitis may have mild pain and patients with mild esophagitis may have severe pain. The burning is aggravated by bending, stooping or lying down and on drinking hot liquids or alcohol. It is usually be relieved by antacids.
- Reflux into the pharynx, larynx, and tracheobronchial tree can cause chronic cough, bronchoconstriction, pharyngitis, laryngitis, bronchitis, or pneumonia.
- Dysphagia may develop due to stricture of lower end of esophagus or development of adenocarcinoma in Barrett's esophagus.
- Mucosal erosions may produce bleeding, hematemesis and anemia.

Differentiating GERD from Angina

Table 4.9 Differentiating GERD from angina

GERD	Angina
• Burning pain	• Gripping or crushing pain
• Pain produced by bending, stooping or lying down	• Pain produced by exercise
• Pain relieved by antacids	• Pain relieved by rest and nitrates
• Radiates to retrosternal area and not to shoulders and arms	• Pain radiates into neck, shoulders and both arms
• No dyspnea, sweating and tachycardia	• Accompanied by dyspnoea, tachycardia and sweating

Investigations

- A history of recurrent heartburn and response to antacids or acid-suppressant medication is adequate to diagnose GERD. Investigations are reserved for patients with alarm symptoms such as dysphagia, weight loss, or gastrointestinal bleeding.

- *Endoscopy* is used to confirm damage to esophagus or to rule out other alternate pathology.
- *Barium swallow* followed by X-rays in the head-down position can detect movement of barium from stomach to esophagus suggesting reflux.
- *24-hour esophageal pH monitoring* is the gold standard test for identifying reflux. This is done by fixing a small pH probe in the esophagus, 5 cm above the LES, and recording all episodes of acid reflux (drop in pH <4) over a 24-hour period. Total number and duration of each reflux event yield a total esophageal acid contact time
- *Bernstein test* can tell whether the symptoms are due to acid reflux. This test is done by perfusing acid (0.1 N Hcl, pH 1.1) or saline (control) through a catheter positioned in mid-esophagus. If symptoms develop during acid, but not saline perfusion, the test is considered positive for GERD.
- *Resting and stress ECG* to rule out angina.

Complications of GERD

- Esophagitis
- Peptic stricture
- Barrett esophagus
- Carcinoma of esophagus
- Aspiration pneumonia.
- Iron deficiency anemia due to chronic blood loss from esophageal ulcers.

Treatment

General Measures

- Weight reduction if overweight, head end elevation of the bed at night, reduction in alcohol consumption and cessation of smoking help all patients with GERD.

Medical Management

- This is the preferred treatment. The goal of treatment is to relieve symptoms and prevent complications. Most patients obtain symptom relief with the following treatment, but symptoms usually return when treatment is stopped and long-term therapy is then required.
- *Antacids*: Antacids neutralize the acid in the stomach and immediately relieve heart burn. Most antacid preparations contain combination of magnesium sulphate and aluminium hydroxide. Magnesium sulphate tends to cause diarrhea while aluminium hydroxide causes constipation. Combining both of them will have neutral effect on bowel movements. Antacids are available in both liquid and tablet forms. These preparations can be taken as and when required (10 ml 3 to 6 times daily). Alginate-containing antacids form a gel or 'foam raft' on top of gastric contents and thereby reduce reflux.
- *H_2-receptor antagonists* (e.g. cimetidine, ranitidine, famotidine and nizatidine) are used for acid suppression along with antacids. They should be given for 6–8 weeks.
- *Proton pump inhibitors* (PPIs) (e.g. omeprazole, rabeprazole, lansoprazole, pantoprazole, esomeprazole): they inhibit gastric hydrogen/potassium-ATPase and reduce gastric acid secretion by 90%. These are more effective than H_2 blockers and are preferred over them. 8 weeks of therapy can heal erosive esophagitis in up to 90% of patients. Patients with severe symptoms need prolonged treatment, often for years. Rebound increased acid secretion is a problem with these agents.
- *Prokinetic agents* (metoclopramide, mosapride, cintapride and domperidone). They increase lower esophageal sphincter tone and speed gastric emptying. They are only occasionally helpful. Cisapride increases QT interval and predisposes to cardiac arrhythmias. It has been withdrawn from market.

Surgery

- Antireflux surgery can be considered for patients with severe reflux symptoms confirmed by pH monitoring and with esophagitis on esophagoscopy. But even these patients respond to medical therapy which should be reinforced. Surgery can also be an alternative for patients who require long-term, high dose PPIs.
- In antireflux surgery, the gastric fundus is wrapped around the esophagus (modified Nissen fundoplication), which increases lower esophageal sphincter pressure and prevents reflux. Laproscopic fundoplication is another procedure for GERD.
- Complications of GERD like stricture require repeated dilatations or surgical resection.

Q. Barrett's esophagus.

- This is metaplasia of esophageal squamous epithelium to columnar epithelium.
- It is a complication of long standing severe reflux esophagitis and is a risk factor for developing esophageal adenocarcinoma. Barrett's epithelium progresses through a dysplastic stage before developing into adenocarcinoma.
- Metaplastic columnar epithelium develops because it is more resistant to acid-pepsin damage than squamous epithelium.
- It is more common in men and older age groups.
- Endoscopically, Barrett's epithelium may be seen as a continuous sheet, a finger-like projection into the esophagus or as islands of columnar mucosa.

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- An indocarmine spray down the endoscope can detect intestinal metaplasia and possibly dysplasia. Biopsies should be obtained from all four quadrants of the Barrett's segment.

Treatment

- Esophagectomy to remove the metaplastic segment appears to be a logical step, but the morbidity and mortality of this surgery are very high compared to low risk of developing malignancy (0.5% per year). Moreover regular endoscopy can detect dysplasia before development of adenocarcinoma. Hence, instead of surgery, endoscopic surveillance every 2 to 3 years, with four-quadrant biopsies of Barrett's segment is recommended nowadays.
- If high-grade dysplasia is found on biopsy, esophagectomy of the involved segment is adviced before it turns into adenocarcinoma. Photodynamic laser or thermo-coagulative mucosal ablation and endoscopic mucosal resection are being evaluated as alternatives.
- There is no evidence that treatment with PPIs or anti-reflux surgery leads to Barrett's regression.

Q. Define dysphagia. What are the causes of dysphagia? How do you approach a case of dysphagia?

- Dysphagia means difficulty in swallowing. Odynophagia is pain while swallowing.
- Swallowing is a process governed by the swallowing center in the medulla, and in the mid-esophagus and distal esophagus by a largely autonomous peristaltic reflex coordinated by the enteric nervous system.

Etiology

Table 4.10 Etiology of dysphagia

Congenital
- Congenital stenosis of esophagus
- Tracheoesophageal fistula
- Congenital web

Acquired

A. Causes in the esophageal wall
- Strictures
- Carcinoma esophagus
- Diverticulum
- Esophagitis (reflux, Candida)
- Achalasia cardia
- Plummer-Vinson syndrome
- Scleroderma

(*contd.*)

B. Causes outside the esophagus
- Thyroid swelling
- Secondaries in the neck
- Mediastinal mass, lymphadenopathy, or absess
- Aortic aneurysm
- Left atrial enlargement
- Osteophytes in cervical spine

C. Painful diseases of mouth and pharynx
- Stomatitis
- Tonsillitis
- Pharyngitis
- Retropharyngeal abscesses
- Diphtheria

D. Motility disorders
- Achalasia cardia
- Scleroderma
- Diffuse esophageal spasm
- Hypertensive lower esophageal sphincter

E. Neuromuscular disorders
- Bulbar paralysis
- Pseudobulbar palsy
- Myasthenia gravis
- Multiple sclerosis
- Parkinson's disease
- Rabies

F. Functional
- Functional dysphagia

Approach to a Case of Dysphagia

History

- The type of food causing dysphagia gives useful information. Dysphagia only for solids implies mechanical dysphagia with partial obstruction. Dysphagia for both solids and liquids occurs in neuromuscular and severe obstructive leisons.
- H/o difficulty in initiating swallowing suggests oropharyngeal dysphagia. H/o food "sticking" after swallowing indicates esophageal dysphagia.
- The duration and course of dysphagia are also helpful in diagnosis. Transient dysphagia is usually due to an inflammatory process. Sudden onset dysphagia occurs due to obstructive foreign bodies. Progressive dysphagia may be due to carcinoma esophagus or scleroderma or achalasia. Intermittent dysphagia is seen in esophageal spasm.
- Dysphagia with nasal regurgitation is seen in pharyngeal paralysis.
- H/o regurgitation of old food and halitosis suggests Zenker's diverticulum.
- Tracheobronchial aspiration with dysphagia is seen in tracheoesophageal fistula.

- Weight loss and progressive dysphagia in elderly is highly suggestive of carcinoma. When hoarseness precedes dysphagia, the primary lesion is usually in the larynx. When hoarseness appears after dysphagia it suggests involvement of the recurrent laryngeal nerve by extension of esophageal carcinoma. Sometimes hoarseness may be due to laryngitis secondary to gastroesophageal reflux.
- Chest pain with dysphagia occurs in diffuse esophageal spasm and related motor disorders.
- A prolonged history of heartburn preceding dysphagia indicates peptic stricture.
- If odynophagia is present, it suggests esophagitis.

Physical Examination

- Pallor is present in Plummer-Vinson syndrome due to iron deficiency.
- Neck should be examined for thyromegaly, lymphadenopathy or any other abnormality.
- Mouth and pharynx should be examined for any local pathology.
- Skin should be examined for evidence of scleroderma.
- Neurological examination should be done looking for evidence of bulbar or pseudobulbar palsy.
- Abdomen should be examined for any distension, mass.
- Cancer spread to lymph nodes and liver may be evident.
- Respiratory system examination may reveal complications of dysphagia such as aspiration pneumonia.

Investigations

- Hemoglobin and peripheral smear for anemia.
- Barium swallow detects tumours as filling defects and strictures as rat tail appearance.
- Endoscopy and biopsy of any lesions.
- Esophageal motility studies.
- Chest X-ray to rule out mediastinal mass or bronchogenic Ca.
- CT scan of neck and chest to rule out any mass lesions.

Q. Plummer-Vinson syndrome (Paterson-Kelly's syndrome).

- The combination of symptomatic hypopharyngeal webs and iron-deficiency anemia is called Plummer-Vinson syndrome.
- It is usually seen in middle-aged women.
- Esophageal webs are thin, diaphragm-like membranes of squamous mucosa. They are usually seen in the mid or upper esophagus and may be multiple.
- Most cases are asymptomatic. Solid food dysphagia may occur. Dysphagia is intermittent and not progressive.
- Investigations include barium esophagogram and endoscopy.
- Treatment involves passage of a large (>16 mm diameter) bougie dilator to disrupt the lesion. Repeated dilations are required in many patients. Underlying iron deficiency should be treated.

Q. Define hiccups (singultus). What are the causes of hiccups? Add a note on its treatment.

Definition

- A hiccup is an involuntary, intermittent contraction of the diaphragm and the inspiratory intercostal muscles that results in a sudden inspiration and ends with abrupt closure of the glottis.
- Hiccups have no known physiological function. They are usually benign and self-limiting. However, occasionally they may be a sign of serious underlying illness.

Causes

Table 4.11 Causes of hiccups

A. ***CNS diseases***
Neoplasms, infections, cerebrovascular accident, trauma

B. ***Toxic and metabolic problems***
Alcohol intoxication, uremia, diabetic ketoacidosis, hyponatremia

C. ***Irritation of the vagus or phrenic nerve***
- Sudden temperature changes (hot then cold liquids, hot then cold shower)
- Foreign body in ear
- *RS*: Pneumonia, empyema
- *CVS*: Myocardial infarction, pericarditis, aneurysm, reflux esophagitis
- *Abdomen*: Subphrenic abscess, hepatitis, pancreatitis, cholecystitis, gastric or pancreatic malignancy, sudden gastric distension (carbonated beverages, air swallowing, overeating)

D. ***Surgical***
General anesthesia, postoperative

E. ***Psychogenic***
Excitement, stress, laughing

F. ***Idiopathic***

Investigations

- Most cases of hiccups are benign and require no investigations.
- Persistent hiccups (lasting >48 hrs) require detailed neurologic examination, serum creatinine, liver function tests, and a chest X-ray.
- If the cause is still not clear, CT of the head, chest, and abdomen, echocardiography, bronchoscopy, and upper

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GI scopy may help. Chest fluoroscopy helps in studying diaphragmatic movement and diagnosing unilateral hiccups.

Treatment

- Idiopathic hiccups can often be terminated by simple measures such as stimulation of nasopharynx, pressure on eyeballs, breath holding, Valsalva's maneuver, sneezing, or rebreathing into a bag, stimulation of the vagus by carotid massage.
- If there is gastric distention, it should be relieved by belching or insertion of a nasogastric tube.
- *Drugs*: Many drugs can help to control hiccups.
  Chlorpromazine, 25–50 mg orally or intramuscularly
  Baclofen 10 mg TID

  Other useful drugs are metoclopramide, domperidone, phenytoin, diazepam, and gabapentin.

Q. Define dyspepsia. What are causes of dyspepsia? How do you investigate and manage a case of dyspepsia?

- Dyspepsia is pain or discomfort in the upper abdomen especially in the epigastrium. Patient may describe it as abdominal fullness, early satiety, burning, bloating, belching, nausea, retching, or vomiting.

Rome III criteria for dyspepsia

- One or more of the following symptoms:
  - Postprandial fullness (termed postprandial distress syndrome).
  - Early satiation (meaning inability to finish a normal sized meal or postprandial fullness).
  - Epigastric pain or burning (termed epigastric pain syndrome)
- Ulcer dyspepsia is dyspeptic symptoms associated with peptic ulcer.
- Non-ulcer dyspepsia is dyspepsia without any identifiable cause.
- Many cases of dyspepsia are associated with *H. pylori* infection.

Causes of Dyspepsia

- ***Food related:*** Overeating, eating high-fat foods, drinking too much alcohol or coffee.
- ***GI tract problems***: Peptic ulcer, GERD, gastric cancer, gastroparesis (in diabetes mellitus), infections (*Helicobacter pylori*, Giardia, Strongyloides).
- ***Pancreatic diseases***: Pancreatic carcinoma, chronic pancreatitis.
- ***Biliary tract disease***: Cholelithiasis.
- ***Other conditions***: Diabetes, renal insufficiency, myocardial ischemia, hiatus hernia and pregnancy.
- ***Drugs***: NSAIDs—metformin, corticosteroids, erythromycin.
- ***Functional or "nonulcer" dyspepsia***: Most common cause of chronic dyspepsia. Most patients have no identifiable reason.

Differential Diagnosis

Peptic Ulcer Disease

- Discomfort occurs predominantly in the epigastrium, but can also occur in the right or left upper quadrants or the hypochondrium.
- Pain is usually burning type or hunger-like in quality. It can be vague or cramping.
- Gastric ulcer pain is aggravated by food while duodenal ulcer symptoms occur two to five hours after meals or on an empty stomach. Symptoms also occur at night, between 11 pm and 2 am, when the circadian stimulation of acid secretion is maximal.
- Antacids, H_2 blockers and proton pump inhibitors relieve the pain.

Gastroesophageal Reflux Disease

- Most common symptoms of GERD are heartburn and regurgitation.
- Symptoms are aggravated by stooping or lying flat and relieved by antacids.

Gastric Malignancy

- Usually occurs in patients over 50 years of age.
- Other features include progressive dysphagia, weight loss, hematemesis, anemia, persistent vomiting and abdominal mass.

Biliary Tract Disease

- Dull aching pain in the epigastrium or right upper quadrant. Pain may radiate to the back or scapula.

Pancreatitis

- Pain is mainly in the epigastric region, severe and dull aching. It often radiates to back and associated with nausea and vomiting, It increases on lying down and decreases by bending forward.

Irritable Bowel Syndrome

- Chronic abdominal pain and altered bowel habits in characteristic of IBS.

Drug Induced Dyspepsia

- Dyspeptic symptoms appear after the intake of offending drugs.

Investigations

- If the patient is less than 50 years, he is likely to be having functional dyspepsia hence empiric therapy with H_2 blockers (ranitidine, famotidine) or proton pump inhibitors (omeprazole, pantoprazole) may be tried.
- However, if the history or examination is pointing towards any specific cause listed above investigations should be done to rule out the same.
- Ultrasound abdomen and CT abdomen is helpful to rule out pancreatic or biliary tract disease.
- Esophageal pH monitoring may help if gastroesophageal reflux is suspected.
- Noninvasive tests for *H. pylori* (IgG serology, fecal antigen test, or urea breath test) help in ruling out *H. pylori* infection.
- Upper GI scopy should be done in patients above 50 years with persistent dyspepsia and in all patients with "alarm" features such as weight loss, dysphagia, recurrent vomiting, evidence of bleeding, or anemia to rule out carcinoma stomach.

Treatment

- If any underlying cause is found, it should be treated.
- For non-ulcer dyspepsia, 2 to 4 weeks of therapy with H_2 blockers (ranitidine, famotidine) or proton pump inhibitors (omeprazole, pantoprazole) may be tried.

Q. Discuss the etiology, clinical features, investigations and management of non-ulcer dyspepsia (functional dyspepsia; idiopathic dyspepsia).

- Non-ulcer dyspepsia is defined as chronic dyspepsia (pain or upper abdominal discomfort) in the absence of organic disease.

Etiology

- Exact etiology is unknown. However following factors have been implicated.
  - Abnormal gastric motor function (delayed gastric emptying, reduced gastric compliance)
  - Visceral hypersensitivity
  - *Helicobacter pylori* infection
  - Psychosocial factors (anxiety, somatization, neuroticism, and depression)

Clinical Features

- Patients are usually young (<40 years) and women are affected twice as commonly as men.
- Patients c/o postprandial fullness, early satiation, and epigastric pain. Any one or more of these symptoms may be present.
- Morning symptoms are characteristic and pain or nausea may occur on waking.
- Symptoms of irritable bowel syndrome such as pellet-like stools and feeling of incomplete evacuation after defaecation may be present.
- Examination is usually normal except for epigastric tenderness. There is no weight loss. Patients often appear anxious.
- A drug history (NSAIDs) should be taken and depressive illness should be ruled out.

Investigations

- All organic causes should be ruled out by appropriate tests.
- Alarming features which merit thorough investigations include dysphagia, anemia, weight loss, anorexia, dysphagia and hematemesis or melena.
- In women, pregnancy should be ruled out by urine pregnancy test and ultrasound.
- Upper GI scopy to rule out peptic ulcer, malignancy and hiatus hernia.
- Ultrasound abdomen if required to rule out gallstone disease and other mass lesions.
- Tests to rule out *H. pylori* infection.

Management

- Explain the nature of illness and reassure.
- Address any underlying psychological stress.
- Avoid cigarette smoking and alcohol abuse. Reduce intake of fatty foods.
- Antacids are sometimes helpful.
- Prokinetic drugs such as itopride, metoclopramide (10 mg 8-hourly) or domperidone (10 mg 8-hourly) may be given before meals if nausea, vomiting or bloating is prominent.
- H_2-receptor blockers or proton pump inhibitors may be tried if night pain or heartburn is troublesome.
- Low-dose amitriptyline is sometimes of value especially in patients with underlying psychological stress.
- *H. pylori* should be eradicated if the tests are positive.

Q. Describe briefly esophageal motor disorders.

Q. Achalasia.

- Esophageal motor disorders include:
  - Achalasia
  - Diffuse esophageal spasm
  - Nutcracker esophagus
  - Hypertensive lower esophageal sphincter
  - Scleroderma (systemic sclerosis)

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Achalasia

- Achalasia (a Greek term which means "does not relax") is a disease of unknown cause in which there is a loss of peristalsis in the distal esophagus and failure of LES (lower esophageal sphincter) relaxation.

Etiology

- There is loss of inhibitory neurons in the distal esophagus leading to impaired relaxation of smooth muscle.
- Primary idiopathic achalasia accounts for most of the patients.
- Secondary achalasia occurs due to malignant infiltration of the esophagus, lymphoma, Chagas' disease, eosinophilic gastroenteritis, and neurodegenerative disorders.

Clinical Features

- Achalasia affects patients of all ages and both sexes.
- Dysphagia, chest pain, and regurgitation are the main symptoms. Dysphagia occurs with both liquids and solids. Aspiration may occur due to regurgitation of retained food and saliva in the esophagus.
- The course is usually chronic, with progressive dysphagia and weight loss over months to years.

Investigations

- *Chest X-ray* may show absence of the gastric air bubble. An air-fluid level in the mediastinum in the upright position represents retained food in the esophagus.
- *Barium swallow* shows proximal esophageal dilation and beaklike narrowing of terminal esophagus.
- *Fluoroscopy* shows loss of peristalsis in the lower two-thirds of the esophagus.
- *Manometry* shows elevated resting esophageal pressure and failure of LES to relax on swallowing. Cholecystokinin (CCK), which causes relaxation of LES in normal people, causes contraction of the LES in achalasia. This happens because of loss of inhibitory neurons.
- *Endoscopy* is helpful in excluding the secondary causes of achalasia, particularly gastric carcinoma.

Treatment

- Nitrates and calcium channel blockers provide short-term benefit. Nitroglycerin, 0.3 to 0.6 mg, or isosorbide dinitrate, 2.5 to 5 mg sublingually or 10 to 20 mg orally is used before meals. The calcium channel blocker nifedipine, 10 to 20 mg orally or sublingually before meals, is also effective.
- Endoscopic injection of botulinum toxin into LES can provide temporary relief. Botulinum toxin acts by blocking cholinergic excitatory nerves in the sphincter.
- Balloon dilatation and Heller's extramucosal myotomy of the LES, are other effective procedures.

Diffuse Esophageal Spasm

- Diffuse esophageal spasm is characterized by non-peristaltic contractions of long duration. This happens due to dysfunction of inhibitory nerves. There is patchy degeneration of nerve cell processes in the esophagus.

Clinical Features

- Diffuse esophageal spasm presents with chest pain and dysphagia. Chest pain is retrosternal and may may radiate to both arms, and the sides of the jaw mimicking the pain of myocardial ischemia. However presence of dysphagia should help distinguish the pain from myocardial ischemia.

Investigations

- Barium swallow shows uncoordinated simultaneous contractions that produce the appearance of "corkscrew" esophagus.
- Manometric studies show increased luminal pressure.

Treatment

- Smooth muscle relaxants such as sublingual nitroglycerin (0.3 to 0.6 mg) or longer-acting agents such as isosorbide dinitrate (10 to 30 mg orally before meals) and nifedipine (10 to 20 mg orally before meals) are helpful.

Nutcracker Esophagus

- This refers to hypertensive esophageal peristaltic contractions. Hypertensive peristaltic contractions may be due to cholinergic or myogenic hyperactivity.
- Patients present with chest pain, dysphagia, or both. Chest pain usually occurs at rest but may be brought on by swallowing. Dysphagia for solids and liquids may occur.
- Investigations and treatment is same as diffuse esophageal spasm.

Hypertensive Lower Esophageal Sphincter

- This refers to spastic contraction of LES and failure to relax. This leads to dysphagia. Investigations and treatment are same as diffuse esophageal spasm.

Scleroderma

- Esophageal involvement is present in up to 90 percent of patients with scleroderma. Scleroderma primarily involves the smooth muscle layer of the gut wall, resulting in atrophy and sclerosis of the distal two-thirds of the esophagus. This produces aperistalsis or low amplitude contractions, and low or absent lower esophageal sphincter pressure.

- The proximal esophagus (striated muscle) is spared and exhibits normal motility.
- Patients commonly present with dysphagia.

Treatment

- Prokinetic drugs such as metoclopramide and mosapride increase esophageal sphincter pressure, improve peristalsis, and enhance gastric emptying.
- Erythromycin is also beneficial in scleroderma. It acts as a motilin agonist which increases gastric contractions and lowers esophageal sphincter pressure.

Q. What are the causes of blood and mucus in the stool? How do you investigate such a case?

Table 4.12 Causes of blood and mucus in the stool

Causes of blood plus mucus in the stool	Causes of blood in the stool
• ***Dysentery:*** Bacillary, amebic • ***Inflammatory bowel disease:*** Crohn's disease, ulcerative colitis • ***Malignancy of lower GI tract:*** *Ca colon, Ca sigmoid colon and Ca rectum* • *Diverticulitis* • *Necrotizing enterocolitis* • *Mesenteric vascular disease*	• All the above causes • Upper GI malignancy: Ca stomach, Ca esophagus • Peptic ulcer, gastric erosions • Esophageal varices • Lower GI malignancy (Ca colon) • Hemorrhoids

Investigations

- ***Stool:*** Look for gross or occult blood, ova, cysts, trophozoites, WBCs, bacteria. Culture and sensitivity of stool can identify the infecting organism.
- ***Lower GI scopy:*** Can identify tumors, ulcers, diverticula, etc. in the rectum, sigmoid colon and colon.
- ***Barium enema:*** Can identify growths, filling defects, diverticuale and ulcers.
- ***Biopsy:*** Of an ulcer or growth during GI scopy to rule out malignancy or any other pathology.
- ***Ultrasound abdomen:*** Can detect any mass or other pathology in the abdomen.
- ***CT abdomen:*** Can detect any mass or other pathology in the abdomen.

Q. Discuss the etiology, clinical features, investigations and management of peptic ulcer.

- Peptic ulcer is a break in the gastric or duodenal mucosa that arises when there is decrease in mucosal defensive factors or increase in ulcerogenic factors such as acid and pepsin.
- By definition, ulcers extend through the muscularis mucosa and are usually over 5 mm in diameter.
- Peptic ulcers occur more commonly in duodenum than stomach but can also occur in the jejunum after anastomosis to stomach and ileum adjacent to Meckel's diverticulum.
- They are more common in men than women.
- Duodenal ulcers occur commonly between 30 and 55 years of age, whereas gastric ulcers occur commonly between 55 and 70 years of age.

Etiology

Table 4.13 Etiology of peptic ulcer

• *H. pylori* infection (produces mucosal damage) • NSAIDs and aspirin • Gastrinoma (Zollinger-Ellison syndrome) • Systemic mastocytosis (causes excessive acid secretion) • Vascular insufficiency including crack cocaine use (produces mucosal ischemia and damage) • Radiation therapy (mucosal damage)	• Infiltrating diseases (sarcoidosis) • Carcinoid syndrome • Crohn's disease • Stress ulcers • Renal failure • Smoking and alcohol intake • Idiopathic

Pathophysiology

- Most cases of peptic ulcer are due to *Helicobacter pylori* infection and use of nonsteroidal anti-inflammatory drugs (NSAIDs).
- Most duodenal ulcer patients have increased acid secretion whereas acid secretion is normal or even decreased in patients with gastric ulcer. Hence, increased acid may play an important role in the causation of duodenal ulcer and impaired mucosal defense may play an important role in the causation of gastric ulcer.
- NSAIDs inhibit the synthesis of protective prostaglandins which play an important role in the mucosal defense, and lead to ulcer formation.
- *H. pylori* infection is associated with increased gastric acid secretion and decreased duodenal mucosal bicarbonate secretion. This leads to duodenal ulcer. *H. pylori* infection causes chronic inflammation of gastric mucosa which overwhelms the gastric mucosal defense mechanisms and leads to gastric ulcer formation.

Clinical Features

- Epigastric pain (dyspepsia) is the most common symptom of peptic ulcer. However some patients may have silent ulcers which come to attention due to bleeding or

perforation. Pain is well localized, felt in the epigastrium and not severe. It is usually burning type but can also be gnawing, dull, aching, or "hunger-like."

- Pain occurs in episodes (periodicity), lasting 1–3 weeks every time, 3–4 times a year. In between, patient is free of pain.
- The typical pain pattern in duodenal ulcer occurs 1 to 3 hours after a meal and is frequently relieved by antacids or food whereas gastric ulcer pain is worsened by intake of food. Pain that awakes the patient from sleep (between midnight and 3 am) is the most discriminating symptom, and is seen in two-thirds of duodenal ulcer patients and one-third of gastric ulcer patients.
- Nausea and weight loss are common in gastric ulcer whereas weight gain may be present in duodenal ulcer patients because pain relief from food makes them eat more frequently.
- Epigastric pain which becomes constant, and radiates to the back may indicate a penetrating ulcer (pancreas).
- Sudden onset of severe, generalized abdominal pain may indicate perforation.
- Pain worsening with meals, nausea, and vomiting of undigested food suggest gastric outlet obstruction.
- Tarry stools or coffee ground vomitus indicate bleeding from ulcer.
- Physical examination is often normal in uncomplicated peptic ulcer except mild epigastric tenderness. Sometimes pallor may be present due to chronic blood loss from ulcer. In peptic ulcer perforation board like rigidity of abdominal wall is found.

Investigations

Blood Tests

- Anemia may be present due to acute or chronic blood loss from the ulcer. Increased WBC count and increased amylase suggests ulcer penetration into the pancreas. Serum gastrin levels may be high in patients with Zollinger-Ellison syndrome.

Upper GI Scopy

- This is the procedure of choice for the diagnosis of duodenal and gastric ulcers. Biopsy can also be taken during endoscopy. Duodenal ulcers are virtually never malignant and do not require biopsy.

Barium Swallow

- Can be used for screening patients with uncomplicated dyspepsia. However, it is less commonly used now because of wide availability of endoscopy.

Tests for H. pylori

- Mucosal biopsies can be obtained during endoscopy for rapid urease test and for histologic examination. Noninvasive tests for *H. pylori* include fecal antigen assay and urea breath test.

Complications of Peptic Ulcer

- Hemorrhage
- Perforation
- Ulcer penetration
- Gastric outlet obstruction due to scarring.

Differential Diagnosis

- Peptic ulcer disease must be distinguished from other causes of epigastric distress (dyspepsia).

Treatment

- The goal of treatment is to provide relief of symptoms (pain or dyspepsia), promote ulcer healing, and ultimately prevent ulcer recurrence and complications.

General Measures

- Avoid smoking and spicy food.
- Cut down or quit alcohol intake.
- Avoid aspirin and NSAIDs

Table 4.14 Differences between gastric and duodenal ulcer

Factors	Gastric ulcer	Duodenal ulcer
Age	50 – 70 years	30–50 years
Sex	Equal in both sexes	More in males
Acid secretion	Normal or decreased	Increased
Course of the illness	Less remittent	More remittent
Episodes of pain	Immediately after food	Occur 1 to 3 hours after a meal
Antacids	Inconsistent relief of pain	Prompt relief of pain
Food	Provokes the pain	Relieves the pain
Night pains	Rare	Common
Effect on weight	Weight loss	Weight gain

Acid Neutralizing/Inhibitory Drugs

Antacids

- They relieve the pain by neutralizing the acid. They are mainly used for symptomatic relief of epigastric pain.
- Commonly used antacids are mixtures of aluminum hydroxide and magnesium hydroxide. Aluminum hydroxide can produce constipation and phosphate depletion; magnesium hydroxide may cause loose stools. Combining both will neutralize the side effects of each other.
- Dose is 15–30 ml 4 to 6 times per day.
- Calcium carbonate and sodium bicarbonate are other potent antacids.

H_2 receptor blockers

- These agents decrease acid secretion. Examples are ranitidine, famotidine, and nizatidine. All are equally effective.
- These agents are given for 4 to 6 weeks.

Proton pump (H^+, K^+-ATPase) inhibitors

- These agents are the most potent acid inhibitory agents available. They covalently bind and irreversibly inhibit H^+, K^+-ATPase which is the final pathway in acid secretion.
- Examples are omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole.
- Mild to moderate hypergastrinemia has been observed in patients taking these drugs. Gastrin levels return to normal levels within 1 to 2 weeks after stopping the drug.

Mucosal Protective Agents

Sucralfate

- Sucralfate is a complex sucrose salt which becomes a viscous paste within the stomach and duodenum in acidic pH. Thus it forms a coating on ulcers and helps in healing. It does not act in alkaline pH. Hence, giving it along with other acid suppressing agents may render it ineffective.

Bismuth-containing preparations

- These agents coat the ulcer, prevent further pepsin/acid induced damage and stimulate prostaglandins, bicarbonate, and mucus secretion.
- Colloidal bismuth subcitrate (CBS) and bismuth subsalicylate (BSS) are the most widely used preparations. These compounds are commonly used as one of the agents in an anti-*H. pylori* regimen.

Prostaglandin Analogues

- These agents enhance mucosal defense and repair. They also enhance mucous bicarbonate secretion and stimulate mucosal blood flow. Example is prostaglandin E_1 derivative misoprostol.
- Misoprostol is contraindicated in pregnant women because it can cause uterine bleeding and contractions.

H. pylori Eradication

- *H. pylori* should be eradicated in patients with documented peptic ulcer disease. *H. pylori* eradication prevents the reccurence of peptic ulcer and also helps in remission of gastric MALT lymphoma. The agents used with the greatest frequency include amoxicillin, metronidazole, tetracycline, clarithromycin, and bismuth compounds. Combination therapy should be used to eradicate *H. pylori*. Treatment should be given for 10–14 days.

Surgical Treatment

- Less commonly used now because of the availability of effective medical therapy.
- Partial gastrectomy with Billroth I anastomosis for gastric ulcer.
- Options for duodenal ulcer are truncal vagotomy plus pyloroplasty, selective vagotomy plus pyloroplasty, and highly selective vagotomy.
- Emergency surgery is indicated in penetrating or perforating peptic ulcers.

Q. Stress ulcers.

- Stress ulcers are mucosal erosions which usually occur in the fundus and body of the stomach, but sometimes develop in the antrum, duodenum, or distal esophagus.
- They are usually shallow but deeper lesions can cause massive hemorrhage and/or perforation.
- Stress ulcers are the most common cause of gastrointestinal (GI) bleeding in intensive care unit (ICU) patients.

Risk Factors for Development of Stress Ulcers

Table 4.15 Risk factors for development of stress ulcers

• Shock	• Burns over 35 percent of total body surface area (Curling's ulcer)
• Sepsis	• Organ transplant recipients
• Hepatic failure	• Prior history of peptic ulcer disease or upper GI bleeding
• Renal failure	• Mechanical ventilation
• Multiple trauma	
• Head or spinal trauma (Cushing's ulcer)	

Pathogenesis

- Erosions begin to develop within hours of major trauma or serious illness. They are thought to result from derangements in the balance between gastric acid

production and mucosal protective mechanisms. Hypersecretion of acid due to excessive gastrin stimulation of parietal cells is seen in patients with head trauma.

- In critically ill patients, increased concentrations of refluxed bile salts or the presence of uremic toxins can denude the glycoprotein mucous barrier and lead to ulcer formation.
- Ischemia in shock, sepsis, and trauma can lead to impaired perfusion of the gut and lead to ulcer formation.

Prevention of Stress Ulcers

- Antacids
- H_2 blockers (ranitidine, famotidine, nizatidine)
- Sucralfate
- Proton pump inhibitors (omeprazole, pantoprazole)
- Prostaglandin analogs (misoprostol)
- Early enteral nutrition.

Q. Role of *Helicobacter pylori* in peptic ulcer.

Q. Tests to detect *Helicobacter pylori*.

Q. *Helicobacter pylori* eradication regimens.

- *H. pylori* is a spiral-shaped, flagellated, gram-negative, urease-producing bacterium. It lives in the mucus layer of stomach. Some bacterial cells are found adherent to the mucosal cells.
- It has several acid resistance mechanisms of which the most important is production of urease enzyme which catalyzes urea hydrolysis to produce buffering ammonia.

Epidemiology

- *Helicobacter pylori* is the most common chronic bacterial infection in humans.
- Prevalence of *H. pylori* is more in developing countries and low socioeconomic groups. Prevalence is high in the older population–presumably acquired in their childhood when hygiene was less good than today.
- Humans are the only important reservoir of *H. pylori*. Colonization is common in childhood institutions suggesting direct person-to-person spread.
- It spreads by fecal-oral or oral-oral route.

Pathogenesis

- *H. pylori* does not invade the mucosa. Instead, it damages the mucosa by disrupting the mucous layer, liberating enzymes and toxins, and adhering to the gastric epithelium. Urease is an important enzyme secreted by it. Urease converts urea into ammonia, thus alkalinising the surrounding acidic medium so that *H. pylori* can survive, but simultaneously produces ammonia-induced mucosal damage.
- H. pylori produces toxins, Vac A (vacuolating toxin) and Cag A (cytotoxic associated protein) as well as urease and adherence factors. *H. pylori* infection produces superficial gastritis characterized by inflammatory cell infiltration of the mucosa. These inflammatory cells release cytokines which damage the mucosa.
- The antral-predominant gastritis is associated with duodenal ulcer, whereas diffuse gastritis is associated with development of gastric ulcer and adenocarcinoma. Antral *H. pylori* colonization diminishes somatostatin-producing cells. Since somatostatin inhibits gastrin release, gastrin level increases leading to high acid production and duodenal ulcer formation. The mucosa appears red endoscopically, and histologically there is epithelial cell damage. In some individuals this chronic superficial gastritis can involve the body of the stomach and this leads to atrophic gastritis.
- *H. pylori* colonization increases the lifetime risk of peptic ulcer disease, gastric cancer, and B cell non-Hodgkin's gastric lymphoma. Smoking increases ulcer and cancer risk in *H. pylori*—positive individuals.

Diseases Caused by *H. pylori*

- Gastroesophageal reflux disease and dyspepsia.
- Gastritis
- Peptic ulcer disease
- Gastric adenocarcinoma
- MALT (mucosal-associated lymphoid tissue) lymphoma

Tests to Detect *H. pylori* Infection

Non-invasive Tests

- ***Carbon-13 urea breath test*:** This is a quick and simple test which can be used as a screening test. The urea is labeled with isotope ^{13}C. The patient drinks a solution of this labeled urea and then blows into a tube. If *H. pylori* urease is present, the urea is hydrolyzed and labeled carbon dioxide is detected in breath samples. The test is very sensitive (97%) and specific (96%). The breath test is also used to demonstrate eradication of the organism following treatment.
  - ***H. pylori fecal antigen test*:** *H. pylori* antigen can be detected in the stool by immunoassay. This is less accurate than urea breath test but useful in children. Can be used to detect post-treatment eradication.
  - ***Serological tests*:** Detect IgG antibodies by enzyme-linked immunosorbent assay (ELISA) or immunoblot. These tests may be positive even after eradication therapy and therefore are not useful for confirming eradication or the presence of a current infection. These are especially useful for epidemiological studies.

Invasive Tests

- These tests require endoscopy
  - ***Biopsy urease test***: Gastric biopsies are added to a urea solution containing phenol red. If *H. pylori* are present, the urease enzyme splits the urea to release ammonia which raises the pH of the solution and causes a rapid colour change.
  - ***Culture***: Biopsies specimens can be cultured and antibiotic sensitivity ascertained.
  - ***Histology***: Biopsy specimens can be stained (Giemsa) and looked for the presence of *H. pylori*.

Treatment

- *There are many triple drug regimens for eradication of H. pylori infection. These are as follows*:
  - Omeprazole, amoxicillin, and clarithromycin (OAC)
  - Bismuth subsalicylate, metronidazole, and tetracycline (BMT)
  - Lansoprazole, amoxicillin, and clarithromycin (LAC)
  - These triple drug combinations come as kits and are given for 10 to 14 days

Q. Define hematemesis. What are the causes of hematemesis? How do you investigate and manage a case of hematemesis?

Q. Causes of upper GI bleeding.

- *Hematemesis* is vomiting of blood which may be obviously red or have an appearance similar to "coffee-grounds". Usually the source of bleeding in hematemesis is GI tract above the ligament of Treitz.

Etiology of Hematemesis

Table 4.16 Etiology of hematemesis

• Peptic ulcers (responsible for the majority of cases) • Esophageal varices due to portal HTN • Portal hypertensive gastropathy • Mallory-weiss tears • Vascular anomalies (hereditary hemorrhagic telangiectasia) • Ca stomach • Ca esophagus • Erosive gastritis (due to NSAIDs, alcohol, or severe medical or surgical illness)	• Erosive esophagitis (due to GERD) • Aortoenteric fistulas • Post-surgical anastamosis • Systemic causes; hemophilia, thrombocytopenia

Clinical Presentation

History

- Vomiting of red blood or coffee ground vomitus. Red blood indicates fresh bleeding and coffee ground indicates bleeding sometime back.
- Patient may give h/o of malena. Malena refers to black, tarry, foul smeeling stool. It occurs when more than 60 ml of blood is lost into the upper GI tract.
- H/o syncopal attack may be present if there is massive bleeding.

Historical and clinical clues suggesting the cause of hematemesis

- NSAID use or previous h/o peptic ulcer or dyspepsia suggests peptic ulcer.
- H/o heavy alcohol ingestion or retching before hematemesis suggests a Mallory-Weiss tear.
- H/o chronic liver disease with portal hypertension suggests esophageal varices as the cause of hematemesis.
- H/o dysphagia and weight loss prior to hematemesis suggests esophageal or gastric malignancy.

Examination Findings

- Heart rate and blood pressure can give an idea of amount of bleed. Significant bleeding leads to tachycardia and postural hypotension. A systolic blood pressure less than 100 mm Hg suggests severe bleeding. Pallor may be present.
- Patient may present in a state of shock with hypotension, cold peripheries, excessive sweating, in severe bleeding.
- Signs of liver disease may be present such as jaundice, and ascites.

Investigations

Complete Blood Count with Differential Count

- Hb, PCV are important to know the amount of bleed. Hemoglobin does not fall immediately after bleeding because hemodilution takes some time (up to 72 h). MCV (mean corpuscular volume) may be low due to development of iron deficiency anemia due to recurrent blood loss.

Coagulation Profile

- Bleeding time, clotting time, and prothrombin time. Sometimes a bleeding diathesis may be the cause of hematemesis or exacerbate bleeding from any underlying lesion.

Blood Grouping and Cross Matching

- This is required because patient may require blood transfusion in case of massive hematemesis.

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Liver Function Tests and Renal Function Tests

- To rule out evidence of liver disease and renal failure. Renal failure (pre-renal azotemia) can occur in case of massive hematemesis and hypotension. Pre-existing renal failure can cause uremic gastropathy and cause hematemesis.

Upper GI Endoscopy

- This is the investigation of choice in hematemesis. It is diagnostic as well as therapeutic.
- Endoscopy can identify the source of bleeding, determine the risk of rebleeding and render endoscopic therapy.

Ultrasound Abdomen

- To identify liver disease such as cirrhosis.

Angiography

- If bleeding persists and endoscopy fails to identify a bleeding site.

Management of Hematemesis

Initial Stabilization

- In patients with significant bleeding, two intravenous lines should be inserted. Blood should be sent for grouping and cross-matching for 2–4 units or more of packed red blood cells.
- Aggressive fluid replacement with normal saline or Ringer lactate should be started till blood is available. In mild to moderate bleeding fluid replacement is enough and blood transfusion is not required.
- A nasogastric tube (Ryle's tube) should be placed in all patients with hematemesis. The aspiration of red blood or "coffee grounds" confirms an upper gastrointestinal source of bleeding. Periodic aspiration of the nasogastric tube can identify ongoing bleeding or rebleeding.
- In actively bleeding patients, platelets are transfused if the platelet count is below 50,000/µl. Uremic patients (who have platelet dysfunction) with active bleeding are given three doses of desmopressin (DDAVP), 0.3 µg/kg intravenously, at 12-hour intervals. Fresh frozen plasma is given if prothrombin time is prolonged and INR (international normalized ratio) is >1.5.

Pharmacological Measures to Control Bleeding

Octreotide or vasopressin infusion

- Continuous intravenous infusion of octreotide (100 µg IV bolus, followed by 100 µg/h) reduces splanchnic blood flow and bleeding pending endoscopy. Octreotide is especially useful for variceal bleed, but can also be used for upper GI bleeding of any cause. Vasopressin can also be used but not as effective as octreotide.

Proton pump inhibitors (PPIs)

- Intravenous proton pump inhibitors (omeprazole, lansoprazole, or pantoprazole) reduce bleeding in patients with peptic ulcer. They can be used in bleeding due to other causes. PPIs also reduce the recurrence of bleeding after endoscopic therapy.

Endoscopic Therapy

- Urgent endoscopy is done in patients with active bleeding not responding to conservative measures. Otherwise it can be done once the patient is hemodynamically stable, usually within 24 hours after admission.
- Hemostasis can be achieved in actively bleeding lesions with endoscopic therapies such as cautery, injection, or ligation. Actively bleeding varices can be treated with sclerosant injection or rubber band application to the bleeding varix. Actively bleeding ulcers, angiomas, or Mallory-Weiss tears can be controlled with either injection of epinephrine, cauterization, or application of an endoclip.

Intra-arterial Embolization or Vasopressin

- Angiographic treatment is used rarely in patients with persistent bleeding even after endoscopic therapy.

Transvenous Intrahepatic Portosystemic Shunts (TIPS)

- Placing a stent from the hepatic vein to the portal vein through the liver reduces portal venous pressure and helps in control of acute variceal bleeding. It is used when endoscopic modalities have failed.

Surgery

- Surgery is indicated in:
  - Severe, life-threatening hemorrhage from peptic ulcer not responsive to other measures.
  - Coexisting reason for surgery (e.g. perforation, obstruction, malignancy)
  - Aortoenteric fistula.

Q. Causes of lower gastrointestinal (GI) bleeding.

Table 4.17 Causes of lower gastrointestinal (GI) bleeding

• Diverticulosis	• Radiation enteritis
• Angiodysplasia	• Polyp
• Radiation-induced telangiectasia	• Carcinoma
• Infections	• Hemorrhoids
• Bowel ischemia	• Ulcer
• Inflammatory bowel disease	• Post-biopsy or polypectomy

Q. Discuss the etiology, classification, clinical features, investigations and management of malabsorption syndrome.

Q. What are the disorders causing malabsorption? How do you approach a case of suspected malabsorption?

- Malabsorption refers to impaired absorption of nutrients.
- Malabsorption occurs mainly due to diseases of small intestine since this is the major site of absorption of nutrients.
- Fat is the most difficut to absorb and hence most malabsorption syndromes have steatorrhea. A stool test for fat is the best screening test for malabsorption.

Table 4.18 Causes of malabsorption

Disorders of luminal phase
- *Enzyme deficiency*: Chronic pancreatitis, cystic fibrosis.
- *Enzyme inactivation*: Zollinger-Ellison syndrome
- *Diminished bile salt synthesis*: parenchymal liver diseases
- *Impaired bile secretion*: Bile duct obstruction, chronic cholestasis
- *Increased bile salt loss*: Ileal disease or resection
- *Reduced luminal availability of specific nutrients*: Intrinsic factor deficiency in pernicious anemia causing B_{12} deficiency
- *Bacterial consumption of nutrients*: Bacterial overgrowth causing vitamin B_{12} deficiency

Disorders of mucosal phase
- *Defects in brush border hydrolysis*: sucrase-isomaltase deficiency, lactase deficiency
- *Defects in mucosal absorption (villous atrophy)*: Celiac sprue, tropical sprue, lymphoma, Whipples disease, radiation enteritis, AIDS, Giardiasis, Crohn's disease

Disorders of postabsorptive, processing phase
- *Defects in enterocyte processing*: Abetalipoproteinemia
- *Defects in lymphatic transport*: Intestinal lymphangiectasia, intestinal tuberculosis

Systemic diseases causing malabsorption
- Thyrotoxicosis (rapid transit through gut)
- Hypothyroidism (impaired intestinal motility, bacterial overgrowth)
- Diabetes mellitus (impaired intestinal motility, bacterial overgrowth)
- Scleroderma (impaired intestinal motility, bacterial overgrowth)

Drugs causing malabsorption
- Antibiotics (vitamin B_{12} and vitamin K deficiency)
- Methotrexate (folic acid antagonist, causes inhibition of crypt cell division)
- Cholestyramine (binds bile salts)
- Laxatives (rapid transit through gut. Liquid paraffin causes fat soluble vitamin deficiency)

Clinical Features

Diarrhea

- Diarrhea is the most common complaint. It is due to the osmotic load received by the intestine because of unabsorbed carbohydrates and solutes.
- Bacterial action producing hydroxy fatty acids from undigested fat also can increase fluid secretion from the intestine, further worsening the diarrhea.

Steatorrhea

- Steatorrhea is due to fat malabsorption.
- The hallmark of steatorrhea is the passage of pale, bulky, and foul smelling stools, which float on top of the toilet water and are difficult to flush. Also, patients find floating oil droplets in the toilet following defecation.

Weight Loss and Fatigue

- Weight loss is due to protein energy malnutrition from malabsorption. Fatigue is due to weight loss plus coexisting anemia.

Flatulence and Abdominal Distension

- Bacterial fermentation of unabsorbed food substances releases gases, such as hydrogen and methane, causing flatulence.
- Flatulence often causes uncomfortable abdominal distension and cramps.

Edema

- Protein malabsorption causes hypoalbuminemia which causes peripheral edema.
- With severe protein depletion, ascites may develop.

Anemia

- Anemia develops due to iron deficiency (microcytic anemia), folic acid or vitamin B_{12} deficiency (macrocytic anemia). Iron deficiency is common in celiac disease. Vitamin B_{12} deficiency is common in Crohn's disease with ileal involvement or ileocecal TB.

Bleeding Disorders

- Bleeding tendency is due to vitamin K malabsorption and decreased production of Vit K dependent clotting factors. Ecchymosis is usually seen but patient can also have melena and hematuria.

Bone Pain and Pathologic Fractures

- This is due to vitamin D deficiency causing osteopenia or osteomalacia.
- Malabsorption of calcium can lead to secondary hyperparathyroidism.

Neurologic Manifestations

- Electrolyte disturbances, such as hypocalcemia and hypomagnesemia, can lead to tetany, manifesting as the Trousseau sign and the Chvostek's sign.
- Vitamin malabsorption can cause generalized motor weakness (pantothenic acid, vitamin D) or peripheral neuropathy (thiamine, Vit B_{12}), a sense of loss for vibration and position (Vit B_{12}), night blindness (vitamin A), and seizures (biotin).

Table 4.19 Summary of features of specific nutrient malabsorption

Carbohydrates: Watery diarrhea, flatulence, acidic stool pH, milk intolerance
Protein: Edema, muscle atrophy, amenorrhea
Fat: Pale, bulky, foul smelling stool which floats on water and difficult to flush. Diarrhea without flatulence. Weight loss

Vitamins
Vitamin A: Follicular hyperkeratosis, night blindness
Vitamin B_{12}: Anemia, neuropathy, subacute combined degeneration of the spinal cord
Vitamin B_1, B_2: Cheilosis, painless glossitis, acrodermatitis, angular stomatitis
Folic acid: Megaloblastic anemia
Vitamin D: Tetany, pathologic fractures due to osteomalacia, muscular irritability
Vitamin K: Bleeding tendency

Minerals and electrolytes
Iron: Anemia, glossitis, pica
Calcium: Tetany, pathologic fractures due to osteomalacia, muscular irritability
Zinc: Anorexia, weakness, tingling, impaired taste

Investigations

Imaging Studies

- ***Endoscopy*:** Upper GI scopy is helpful to visualize stomach, duodenum and upper jejunum. A cobblestone appearance of the duodenal mucosa is seen in Crohn's disease. Reduced duodenal folds and scalloping of the mucosa may be seen in celiac disease. Small bowel biopsy can also be taken during endoscopy.
- ***CT and ultrasound abdomen*:** May be helpful in the diagnosis of chronic pancreatitis and other abnormalities in the abdomen.
- ***Barium studies*:** An upper gastrointestinal series with small bowel follow-through or enteroclysis (a double contrast study performed by passing a tube into the proximal small bowel and injecting barium and methylcellulose) can provide information about the gross morphology of the small intestine. For example, small bowel diverticula and mucosal abnormalities can be identified.
- ***Wireless capsule endoscopy*:** Wireless capsule endoscopy allows for visualization of the entire small bowel. Because of the risk of retention, it should be avoided in patients with suspected small bowel strictures.

Tests for Fat Absorption

- ***Fecal fat estimation*:** Increase in stool fat excretion is known as steatorrhea. A 72-hour fecal fat estimation can detect steatorrhea. More than 6 g/day of fat in stool is pathologic.
- ***Sudan III stain*:** Sudan stain on a spot stool sample can detect more than 90 percent of patients with steatorrhea.
- Measurement of fat soluble vitamin levels in the blood (A, D, E, K); prothrombin time.
- ***Near infrared reflectance analysis (NIRA)*:** This may become the procedure of choice in future. NIRA can simultaneously measure fecal fat, nitrogen, and carbohydrates in a single sample.
- ***14C-triolein breath test*:** The test involves measurement of breath CO_2 after ingestion of the radiolabeled triglyceride triolein, and provides a measure of fat absorption.

Tests for Carbohydrate Absorption

- ***Oral glucose tolerance test*:** There will be failure of blood glucose levels to rise after glucose loading.
- ***D-xylose test*:** Patient ingests 25 g of D-xylose, and urine is tested for the presence of D-xylose. Excretion of lesser amounts of D-xylose suggests abnormal absorption (as in celiac sprue).
- ***Lactose tolerance test*:** After ingestion of 50 g lactose, blood glucose levels are monitored. Insufficient increase in blood glucose plus the development of symptoms is diagnostic of lactose intolerance. Another test is measurement of breath hydrogen after lactose ingestion. An increase in breath hydrogen is diagnostic.
- ***Breath tests*:** Breath tests using hydrogen, $14CO_2$, or $13CO_2$ can be used to diagnose specific forms of carbohydrate malabsorption (e.g. lactose, fructose, sucrose isomaltase and others). All of these breath tests rely on bacterial fermentation of nonabsorbed carbohydrate and therefore concurrent antibiotic administration often alters the results.

Tests for Protein Absorption

- Serum albumin will be low.
- Intravenous radioactive chromium is used to label circulating albumin. In case of protein losing enteropathy radioactivity appears in stools.
- Measurement of nitrogen in the stool will be more than 2.5 gm.

- Excretion of alpha-1 antitrypsin in the stool (normally it is absent in the stool).

Tests for Absorption of other Substances

- Complete blood count (anemia), serum iron, ferritin, folate, vitamin B_{12} level, Schilling test (for Vit B_{12} malabsorption), serum calcium, sodium, potassium, β-carotene, and prothrombin time should be obtained in all patients with suspected malabsorption.

Tests for Bacterial Overgrowth

- The gold standard for diagnosis of bacterial overgrowth is the direct quantitative measurement of bacterial counts from aspirated intestinal fluid. However this is invasive and hence the following tests are used more commonly.
- ***Hydrogen breath test*:** This is used to detect bacterial overgrowth in the intestine. Oral lactulose or glucose is metabolized by bacteria with the production of hydrogen. An early rise in the breath hydrogen indicates bacterial overgrowth in the small intestine.
- ***14C-glycocholic acid breath test*:** It is rarely done now and has been replaced by the hydrogen breath test. Patient is given radiolabelled bile acid (14C-glycocholic acid) orally. Bacteria in the intestine deconjugate the bile acid, releasing [14C]-glycine, which is metabolized and appears in the breath as $14CO_2$.

Serologic Tests

- IgA endomysial antibody and IgA anti-tTG antibody both are found in celiac disease. IgG or IgA antigliadin antibodies are also present in celiac sprue.

Intestinal Mucosal Biopsy and Histopathology

- Villous atrophy is seen in celiac disease, and tropical sprue.

Treatment

- Treat the underlying cause.
- Avoid milk and milk products in lactose intolerance.
- Gluten-free diet in celiac disease.
- Pancreatic enzyme supplements in pancreatic insufficiency.
- Reduction of long chain fatty acids and low fat diet in fat malabsorption.
- Antibiotics are the therapy for bacterial overgrowth.
- Corticosteroids, anti-inflammatory agents, such as mesalamine, are used to treat inflammatory bowel disease such as Crohn disease.
- Replacement of specific nutrients which are deficient such as folic acid, iron and Vit B_{12}, Vit D, etc.
- Caloric and protein replacement.

Q. Schilling test.

- This test is performed to determine the cause for vitamin B_{12} malabsorption. Vitamin B_{12} is absorbed in the terminal ileum.
- Causes of vitamin B_{12} malabsorption are intrinsic factor defficiency, atrophic gastritis, small intestinal bacterial overgrowth, exocrine pancreatic insufficiency, and ileal disease.
- Schilling test is performed by administering 1 mcg of radiolabelled Vit B_{12} orally, followed by an intramuscular injection of 1000 microgram of Vit B_{12} one hour later to saturate Vit-B_{12} binding sites so that absorbed radio-labelled B_{12} is excreted in the urine.
- A 24-hour urine is then collected for determination of the percent excretion of the oral dose. Normally at least 10% of the radiolabeled vitamin B_{12} is excreted in the urine. In patients with pernicious anemia or with deficiency due to impaired absorption, less than 10% of the radiolabeled vitamin B_{12} is excreted.
- Next, the above step is repeated after the addition of intrinsic factor. If this second urine collection is normal, it proves intrinsic factor deficiency or pernicious anemia.
- If urinary excretion of Vit B_{12} is still less than 10% after adding intrinsic factor, then the test is repeated after a course of antibiotics. Small intestinal bacterial overgrowth is suggested if an abnormal test is normalized after a course of antibiotics. If the absorption is abnormal even after addition of intrinsic factor and exclusion of bacterial overgrowth, it suggests terminal ileal disease. The Schilling test can also be abnormal in pancreatic insufficiency and celiac disease. Normalization after pancreatic enzyme substitution or a gluten-free diet is useful for diagnosis of these causes of malabsorption.
- The Schilling test can also be used to determine the functional integrity of the ileal mucosa after treatment of ileal Crohn's disease.
- Many labs have stopped doing the Schilling test, due to lack of production of radiolabeled-B_{12} test substances. Also, the treatment remains same (i.e. injection of Vit B_{12}), even if the exact cause were identified. Hence, it is not being performed now.

Q. Celiac sprue (celiac disease, gluten-sensitive enteropathy).

Q. Dermatitis herpetiformis.

- Celiac disease is an inflammatory condition of the small intestine precipitated by the ingestion of wheat, rye, and barley in individuals with genetic predispositions.

- It occurs throughout the world but common in Northern Europe. There is increased incidence of celiac disease within families but the exact mode of inheritance is unknown.

Etiology

- Inflammatory damage to the intestinal mucosa is due to gluten protein of wheat. Gluten is also present in barley, rye and oats. The toxic component in gluten is gliadin.
- Over 90% of patients will have HLA-DQ_2. However environmental factors also play an important role.

Pathogenesis

- Glutens are partially digested in the intestinal lumen to release gliadin and other peptides.
- Gliadin is rich in glutamine. Some of the glutamines in gliadin are deamidated by the enzyme tissue transglutaminase (tTG), generating negatively charged glutamic acid residues.
- These altered gliadin peptides are recognized by local intestinal T cells as foreign, thereby stimulating an immune response. B-cells are also activated and produce various antibodies such as antigliadin, antiendomysial, and anti-tissue transglutaminase (tTG) antibodies.
- This immune response causes damage to intestinal mucosa resulting in maldigestion and malabsorption of food nutrients.

Pathology

- The mucosa of the jejunum is predominantly affected, and the damage decreases towards the ileum.
- There is absence of villi, making the mucosal surface flat. Histological examination shows crypt hyperplasia with chronic inflammatory cells in the lamina propria and subtotal villous atrophy. In the lamina propria there is an increase in lymphocytes and plasma cells.

Clinical Features

- Celiac disease can present at any age but usually in infancy after weaning on to gluten-containing foods. It has a female preponderance.
- Many patients present with anemia or osteoporosis without gastrointestinal symptoms. These individuals usually have proximal intestinal disease that impairs iron, folate, and calcium absorption.
- Patients with significant mucosal involvement present with diarrhea, abdominal distension and bloating after eating, weight loss or growth retardation, and features of vitamin and mineral deficiencies. All nutrients, electrolytes, fat-soluble vitamins, calcium, magnesium, iron, folate, and zinc, are malabsorbed. Diarrhea is due to decreased surface area for water and electrolyte absorption and the osmotic effect of unabsorbed luminal nutrients.
- There is an increased incidence of other autoimmune diseases, like thyroid disease, type-1 diabetes, primary biliary cirrhosis and Sjögren's syndrome.
- Extraintestinal manifestations of celiac disease include rash (dermatitis herpetiformis), neurologic disorders (myopathy, epilepsy), psychiatric disorders (depression, paranoia), and reproductive disorders (infertility, spontaneous abortion).

Investigations

- ***Duodenal/jejunal biopsy***: Shows characteristic changes of celiac sprue.
- ***Serologic markers***: Useful in supporting the diagnosis. An immunoglobulin A anti-tissue transglutaminase (IgA-tTG) antibody, detected by ELISA is the best first test for suspected celiac sprue. Antigliadin IgA and IgG antibodies are sensitive but not specific. Antiendomysial IgA antibodies are highly sensitive and specific for celiac disease.
- ***Tests for malabsorption of proteins, carbohydrate, fat and vitamins***: All patients with celiac disease should be screened for vitamin and mineral deficiencies and have bone densitometry.

Treatment

- Treatment consists of a lifelong gluten-free diet. Wheat, rye, and barley should be excluded from the diet.
- A lactose-free diet is also recommended until symptoms improve because of secondary lactase deficiency.
- Any deficient vitamins and minerals should be replaced. Women of childbearing age should be given folic acid supplements.
- 90% of patients on gluten-free diet experience symptomatic improvement within 2 weeks. A small percentage of patients do not improve on a strict gluten-free diet (refractory sprue). Such patients may have atrophic mucosa. Lymphoma should be ruled out in refractory sprue. Steroids may be of help in refractory sprue if there is persistent inflammation.

Complications

- Intestinal lymphoma
- Ulcerative jejunitis

Dermatitis Herpetiformis

- Dermatitis herpetiformis is the most common skin disorder associated with celiac disease. The presence of dermatitis herpetiformis is pathognomonic of celiac sprue.

- It is characterized by an itchy papular vesicular eruption on the skin. These blisters rupture due to scratching, dry up, and leave an area of pigmentation and scarring.
- The diagnosis can be confirmed by the demonstration of granular IgA deposition in the skin in an area not affected by blistering.
- Treatment includes dapsone in addition to gluten free diet.

Q. Tropical sprue.

- Tropical sprue is a chronic diarrheal disease, possibly of infectious origin, that involves the small intestine and is characterized by malabsorption of nutrients, especially folic acid and vitamin B_{12}.
- It was called tropical sprue because it is common in residents or visitors of a tropical area. Tropical sprue is endemic in most of Asia, some Caribbean islands, Puerto Rico and parts of South America. In India, it is mainly seen in south India. Epidemics of tropical sprue occur, lasting up to 2 years in these areas.

Etiology

- Etiology is unknown, but is likely to be due to an infectious agent because it responds to antibiotics.
- Some of the implicated bacteria include *E.coli*, Klebsiella and Enterobacter.

Clinical Features

- Patients present with diarrhoea, anorexia, abdominal distension and weight loss which can be acute or insidious in onset.

Investigations

- ***Endoscopy and mucosal biopsy***: Endoscopy shows flattening of duodenal folds and "scalloping." The jejunal mucosal biopsy show partial villous atrophy which is usally less severe than celiac disease. Changes are seen in whole of small intestine.
- Other causes of diarrhea must be excluded particularly *Giardia,* which can mimick tropical sprue.

Treatment

- Broad-spectrum antibiotics and folic acid can cure the condition, especially if the patient leaves the tropical area and does not return. Antibiotic treatment involves tetracycline 1 g daily for up to 6 months.

Q. Whipple's disease.

- Whipple's disease is a chronic multisystem disease caused by the gram-positive bacteria *Tropheryma whippelii. Tropheryma whippelii* has high infectivity but low virulence.
- Although the first descriptions of the disorder described a malabsorption syndrome with small intestine involvement, the disease also affects the joints, central nervous system, and cardiovascular system.

Clinical Features

- The disease is common in middle-aged men and affects multiple systems. Onset is insidious and features include diarrhea, steatorrhea, abdominal pain, weight loss, migratory large-joint arthropathy, fever, dementia and ophthalmologic symptoms. It is a major cause of culture negative endocarditis.

Investigations

- Biopsies from the small intestine and other involved organs show presence of PAS-positive (periodic acid-Schiff) macrophages containing the characteristic small bacilli.

Treatment

- The drug of choice is double-strength trimethoprim/sulfamethoxazole for approximately 1 year. Penicillin and chloramphenicol are alternatives.

Q. Protein-losing enteropathy.

- Protein-losing enteropathy is not a specific disease but refers to many disorders characterized by excess protein loss into the gastrointestinal tract.

Causes of Protein-losing Enteropathy

Table 4.20 Causes of protein-losing enteropathy

Gastrointestinal mucosal diseases causing protein loss into GIT
- Ulcerative colitis
- Gastrointestinal carcinomas
- Peptic ulcer
- Amyloidosis
- Celiac sprue
- Whipple's disease
- Ménétrier's disease (hypertrophic gastropathy)

Lymphatic dysfunction
- Intestinal tuberculosis
- Obstruction (enlarged mesenteric nodes or lymphoma)
- Lymphangiectasia

Cardiac disorders
- Heart failure
- Chronic pericarditis

Clinical Features

- There is peripheral edema, low serum albumin and globulin levels in the absence of renal and hepatic disease.

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- Both albumin and globulin are low in protein losing enteropathy. If only albumin is low with normal globulin, search for renal and/or hepatic disease
- Patients with increased protein loss into the gastrointestinal tract from lymphatic obstruction often have steatorrhea and diarrhea.

Diagnosis

- Loss of protein into the gastrointestinal tract can be demonstrated by giving radiolabeled proteins and its quantification in stool during a 24- or 48-h period.

Treatment

- Underlying disease should be treated. For example, gluten-free diet in celiac sprue or mesalamine for ulcerative colitis.

Q. Discuss the etiology, clinical features, investigations, and management of lactose intolerance.

- The term lactose intolerance refers to the development of GI symptoms such as abdominal pain, bloating, flatulence, diarrhea, and vomiting after the ingestion of lactose. It is due to lactase deficiency which hydrolyses lactose into glucose and galactose.
- Intolerance to lactose-containing foods (e.g. dairy products) is a common problem worldwide.

Etiology of Lactose Intolerance

Primary Lactase Deficiency

- Racial or ethnic
- Developmental
- Congenital lactase deficiency

Secondary Lactase Deficiency

- Bacterial overgrowth
- Infectious enteritis
- Giardiasis
- Mucosal injury
- Celiac disease
- Inflammatory bowel disease (especially Crohn's disease)
- Drug- or radiation-induced enteritis

Pathophysiology

- Lactose is hydrolyzed by intestinal lactase to glucose and galactose in the intestine which are then absorbed. If there is lactase deficiency, lactose cannot be hydrolyzed and absorbed. The unabsorbed lactose creates an osmotic load in the intestine, which draws fluid into the intestine. Excess fluid in the intestine causes dilatation of intestine and diarrhea. In the colon, free lactose is fermented by colonic bacteria to yield short-chain fatty acids and hydrogen gas. The combined increase in fecal water, intestinal transit, and generated hydrogen gas accounts for abdominal pain, bloating, flatulence, and diarrhea.

Clinical Features

- Among adults, the age of presentation is 20–40 years.
- *Abdominal pain*: May be crampy in nature and is often localized to the periumbilical area or lower quadrant.
- *Bloating*
- *Flatulence*
- *Diarrhea*: Stools are usually bulky, frothy, and watery.
- Vomiting
- *Borborygmi* may be audible on physical examination and to the patient.

Investigations

Lactose Tolerance Test

- 50 gm of lactose is given orally and blood glucose levels are measured at 0, 1 and 2 hours. An increase in blood glucose by less than 20 mg/dl plus the development of symptoms is diagnostic.
- This test is cumbersome and time consuming, and has largely been replaced by the lactose breath hydrogen test.

Lactose Breath Hydrogen Test

- Oral lactose is given in the fasting state, at a dose of 2 gm/kg (maximum dose, 25 g). Unabsorbed lactose is fermented by intestinal bacteria leading to release of hydrogen gas that is absorbed into the blood and excreted by lungs. Breath hydrogen is sampled at baseline and at 30-minute intervals after the ingestion of lactose for three hours.
- Baseline and post-lactose values are compared. A breath hydrogen value of more than 20 ppm is diagnostic of lactose malabsorption. This is the most common test done.

Genetic Test for Primary Lactose Malabsorption

- Missing gene, coding for lactase may be identified.

Intestinal Biopsy and Measurement of Lactase Enzyme Levels

- This is the "gold standard" test for lactose malabsorption. However, it is not routinely required.

Treatment

Dietary Lactose Restriction

- Initially complete restriction of lactose-containing foods should be tried till the symptoms improve. Improvement of symptoms confirms the diagnosis also.
- Small quantities of lactose may subsequently be reintroduced into the diet, with careful monitoring of symptoms. Many patients will tolerate graded increase in lactose containing foods.

Enzyme Replacement

- Commercially available "lactase" preparations are actually bacterial or yeast beta-galactosidases. They can be taken with food and reduce symptoms in many lactose intolerant subjects.

Probiotics

- Lactase-containing probiotics may be beneficial. However, studies have shown mixed results.

Calcium Supplementation

- Avoidance of milk and other dairy products can lead to reduced calcium intake, which may increase the risk for osteoporosis and fracture. Hence, calcium supplementation should be given to all patients. A dose of 1200–1500 mg/day is necessary for adolescents and young adults.
- In addition, the vitamin D status should also be monitored. If necessary, vit D supplementation should also be given.

Q. Abdominal tuberculosis.

- Abdominal tuberculosis (TB). refers to tuberculosis of intestine, peritoneum and abdominal lymph nodes. One or more of these structures may be affected.
- The most common site of intestinal involvement is the ileocecal region. The affinity of *M. tuberculosis* for this site may be due to its relative stasis and abundant lymphoid tissue.
- Tuberculosis is being seen more frequently in patients with HIV infection.

Etiology

- *Mycobacterium tuberculosis*

Routes of Spread

- Intestinal tuberculosis occurs due to swallowing of infected sputum, or hematogenous spread from active pulmonary or miliary TB, or ingestion of contaminated milk or food, or spread from adjacent organs.

Pathology

Intestinal Tuberculosis

- The macroscopic appearance of the intestinal TB can be categorized into 3 types.

Ulcerative (60%)
- This is characterized by multiple superficial ulcers.
- Ulcers are perpendicular to the long axis of intestine. Healing may result in scarring and stricture formation.
- This pattern has been associated with a virulent clinical course.

Hypertrophic (10%)
- This is characterized by scarring, fibrosis, and hypertrophic mass (pseudotumor).

Ulcerohypertrophic (30%)
- This is characterized by an inflammatory mass centering around the ileocecal valve with thickened and ulcerated intestinal walls.
- It is common in ileocecal TB compared to other segments of intestine.

Peritoneal Tuberculosis

- Peritoneum is studded with tubercles.
- Wet type presents with ascites which develops due to "exudation" of proteinaceous fluid from the tubercles. Most patients have this type.
- Dry type is characterized by fibro-adhesive form of the disease.
- Patients may have combination of both of the above.

Clinical Features

- Constitutional symptoms like anorexia, fatigue, fever, night sweats, and weight loss.
- Nonspecific chronic abdominal pain, diarrhea, constipation, or blood in the stool.
- A doughy mass may be palpable in right lower quadrant of abdomen.
- Abdominal distension due to ascites.
- Patients may also present acutely with small intestinal obstruction and colonic perforation.

Complications of Abdominal Tuberculosis

- Intestinal perforation
- Abscess formation
- Fistula formation (between intestinal loops and into the exterior through skin)
- Malabsorption
- Massive bleeding
- Intestinal obstruction.

4

Differential Diagnosis

- TB must be differentiated from other diseases affecting ileocecal region such as Crohn's disease, *Yersinia enterocolitica, Y. pseudotuberculosis* infection and caecal carcinoma.

Diagnosis

- *Routine laboratory tests* reveal mild anemia, increased ESR and hypoalbuminemia.
- *Chest X-ray* may show evidence of active or old tuberculosis.
- *Plain X-ray* abdomen may show calcified lymph nodes and dilated bowel loops.
- *Tuberculin skin* test is positive in most patients.
- *Ascitic fluid analysis*:
  - High leukocyte count of 150 to 4000/mm^3, with predominant lymphocytes.
  - Fluid is exudative (protein content is >3.0 mg/dl).
  - AFB stain and culture may be positive but have low yield rate.
  - Polymerase chain reaction (PCR) assay can rapidly detect mycobacteria.
  - Adenosine deaminase (ADA) levels in ascitic fluid has high sensitivity and specificity for detecting tuberculosis.
- *Barium meal* and small bowel follow-through may show mucosal ulcerations, strictures (string sign), and hyper-segmented bowel loops.
- *Barium enema* may show deformed cecum, a gaping and incompetent ileocecal valve with narrowing of terminal ileum (inverted umbrella sign).
- *Ultrasound abdomen* may show ascites, thickened ileocecal region, ileocecal mass and lymphadenopathy.
- *CT scan* may show concentric mural thickening of the ileocecal region, with or without proximal intestinal dilatation. Adjacent mesenteric lymphadenopathy may be seen on CT.
- *Colonoscopy* shows ulcers, strictures, nodules, pseudo-polyps, fibrous bands, fistulas, and deformed ileocecal valves.
- *Laparoscopy*: Laparoscopy examination is an effective method of diagnosing peritoneal tuberculosis because it can directly visualize tubercles and biopsy of the peritoneum can be taken. Biopsy specimens may be tested for AFB by staining, culture and PCR.

Treatment

- Treatment is similar to that for pulmonary TB. Conventional antitubercular therapy for at least 6 months including initial 2 months of HREZ (e.g. isoniazid, rifampicin, ethambutol and pyrazinamide) followed by 4 month HR is recommended in all patients.
- Surgery is required for complications such as intestinal perforation, abscess or fistula, massive bleeding, and intestinal obstruction.

Q. What are inflammatory bowel diseases?

Q. Describe the etiology, pathology, clinical features, investigations and treatment of Crohn's disease.

- Inflammatory bowel disease (IBD) is an immune mediated chronic intestinal inflammation. There are two major types of IBD—ulcerative colitis (UC) and Crohn's disease.
- Ulcerative colitis (UC) affects only the colon and Crohn's disease (CD) can affect any part of the GI tract. There is overlap between these two conditions in their clinical, histological and radiological features and sometimes differentiation between the two is not possible. It is possible that these conditions represent two aspects of the same disease.

Crohn's Disease

- Crohn's disease is an idiopathic, chronic inflammatory disease of the gastrointestinal (GI) tract that can affect any part of the tract from the mouth to the anus. It is characterized by exacerbations and remissions.

Epidemiology

- IBD occurs worldwide but more common in the West. Both Crohn's disease (CD) and ulcerative colitis (UC) have an incidence of approximately 5 to 10 per 100 000 annually. Whites are affected more commonly than non-white races. Jews are more affected than non-Jews, and the Ashkenazi Jews have a higher risk than the Sephardic Jews. Crohn's disease is slightly commoner in females (M:F = 1:1.2) and occurs at a younger age (mean 26 years). Ulcerative colitis is more common in males (M:F = 1.2 : 1; mean 34 years).

Etiology

- The exact etiology of IBD is unknown. But the pathogenesis involves three factors: Genetic susceptibility, environmental factors and host immune response. Many risk factors have been identified which are as follows.
- ***Familial and genetic factors***: IBD is more common amongst relatives of patients than in the general population. There is increased concordance for IBD in monozygotic twins than dizygotic twins.

- *Environmental factors*: Good domestic hygiene has been shown to be a risk factor for CD but not for UC. It is suggested that in a clean environment, intestinal immune system is not exposed to many pathogens and hence, may not be able to handle an infection. Hence, even minor infections trigger prominent inflammation.
- *Psychosocial factors*: Major life events such as illness or death in the family, divorce or separation, interpersonal conflict, or other major loss are associated with an increase in IBD symptoms.
- *Nutritional factors*: High sugar and fat intake is suspected to be associated with IBD, but more studies are needed to confirm it.
- *Smoking*: Patients with CD are more likely to be smokers, and smoking has been shown to exacerbate CD. In contrast, there is an increased risk of UC in nonsmokers and nicotine has been shown to be an effective treatment of UC.
- *Appendicectomy*: Appendicectomy is protective for the development of UC, particularly if performed before the age of 20. In contrast, appendicectomy may increase the risk of development of CD.
- *Intestinal microflora*: IBD is characterized by an over-aggressive immune response to luminal bacterial antigens and other products, occurring against a background of genetic susceptibility. There is an alteration in the bacterial flora, with an increase in anaerobic bacteria in CD and an increase in aerobic bacteria in UC.
- *Immunological factors*: Many immunological abnormalities have been described in IBD patients. Many patients lack the ability to appropriately down regulate immune (antigen-specific) or antigen non-specific inflammatory responses to endogenous luminal antigens. There is upregulation of macrophages and T-helper lymphocytes in IBD which release pro-inflammatory cytokines. There is also activation of other cells (eosinophils, mast cells, neutrophils and fibroblasts) which leads to excess production of chemokines (lymphokines, arachidonic acid metabolites, neuro-peptides and free oxygen radicals), all of which can lead to tissue damage.

Pathology

Macroscopic Changes

- Crohn's disease can affect any part of the gastrointestinal tract from the mouth to the anus but commonly affects the terminal ileum and ascending colon (ileocolonic disease).
- The disease is characterized by skip lesions (normal areas in between affected areas).
- The involved small bowel is usually thickened and narrowed. There are deep ulcers and fissures in the mucosa of the intestine, producing a cobblestone appearance.
- Fistulae and abscesses may be seen in the colon.

Microscopic Changes

- In Crohn's disease the inflammation extends through all layers (transmural) of the bowel.
- There is an increase in chronic inflammatory cells and lymphoid hyperplasia.
- Noncaseating granulomas may be seen.

Clinical Features

- It is a chronic disease with remissions and exacerbations.
- The disease may present insidiously or acutely.
- The major symptoms are diarrhea, abdominal pain and weight loss.
- Constitutional symptoms of malaise, lethargy, anorexia, nausea, vomiting and low-grade fever may be present.
- The abdominal pain can be colicky, or felt as discomfort.
- Diarrhea may be associated with blood, making it difficult to differentiate from ulcerative colitis. Steatorrhea may be present due to small intestinal involvement.
- It can present as an emergency with acute right iliac fossa pain mimicking appendicitis.
- It can be complicated by anal and perianal disease and can be the presenting feature, often preceding colonic and small intestinal symptoms by many years.
- Enteric fistulae, e.g. from intestine to bladder or vagina, occur in some cases.
- Examination may show weight loss and general ill-health. Right iliac fossa tenderness and mass are occasionally found. The mass is due either to inflamed loops of bowel that are matted together or to an abscess. Anal fissures or perianal abscesses may be present. Extraintestinal features such as arthritis may be present.

Investigations

Blood Tests

- Anemia is common due to blood loss. ESR, CRP and white cell counts are raised indicating inflammation. Hypoalbuminemia is present in severe disease due to protein loss from intestine. pANCA may be positive in ulcerative colitis.

Stool Examination

- This should be done to exclude infective causes of colitis.

Barium Meal Follow-through

- Examination may show an asymmetrical alteration in the mucosal pattern with deep ulceration, and areas of narrowing or stricturing (string sign).
- Changes are commonly seen in terminal ileum
- Skip lesions with normal bowel in between.

Ultrasound and CT Abdomen

- These are used to define the thickness of the bowel wall and mesentery as well as intra-abdominal and para-intestinal abscesses and also used to rule out alternate pathology in acute presentations.

Radionuclide Scans

- With radiolabelled leucocytes are used to identify small intestinal and colonic disease and to localize extraintestinal abscesses.

Colonoscopy

- Superficial or deep ulceration with cobblestone appearance and deep fissures.
- Skip lesions
- Rectal sparing

Colonic Biopsy

- Can be used to confirm the diagnosis of IBD and exclude other diagnoses. The biopsy characteristically reveals crypt abscesses, branching of crypts, atrophy of glands, and loss of mucin in goblet cells in ulcerative colitis.

Treatment

- The aim of management is to induce and then maintain a remission.

General Measures

- Cigarette smoking should be stopped.
- Diarrhea can be controlled with loperamide or codeine phosphate. Diarrhea in longstanding inactive disease may be due to bile acid malabsorption and responds to cholestyramine.
- Anemia may be due to B_{12}/folic acid or iron deficiency, which should be replaced.

5-ASA (Amino Salicylic Acid) Agents

- The mainstay of therapy for IBD is 5-ASA agents. These agents are effective at inducing remission in both UC and CD and in maintaining remission in UC. It is unclear whether they can maintain remission in CD also. Example is sulfasalazine.
- Sulfasalazine is not broken down in small intestine and the intact molecule reaches colon where it is broken down by colonic bacteria into sulfa and 5-ASA moieties. 5-ASA acts as local anti-inflammatory agent in the colon.
- There are many side effects of sulfasalazine including folate malabsorption. These side effects are due to sulfa moiety. Patients on sulfasalazine should be given folic acid supplements.
- Newer sulfa-free agents such as mesalamine, olsalazine and balsalazide have less of side effects.
- Topical mesalamine enemas are effective in mild-to-moderate distal UC and CD. Mesalamine suppositories are effective in treating proctitis.

Glucocorticoids

- These are effective in patients with moderate to severe UC and CD. Prednisone 40 to 60 mg/d is given for active UC unresponsive to 5-ASA therapy.
- They can be administered intravenously also as hydrocortisone, 300 mg/d, or methylprednisolone, 40 to 60 mg/d. Topically applied glucocorticoids (hydrocortisone enemas or foam) are also effective for distal colitis.
- Glucocorticoids play no role in maintenance therapy of either UC or CD. Once clinical remission has been induced, they should be tapered slowly.

Immunosuppressive Agents

- *Azathioprine, 6-mercaptopurine,* methotrexate and cyclosporine are mainly employed as steroid sparing agents in the management of glucocorticoid-dependent IBD. Tacrolimus and mycophenolate mofetil are newer immunosuppressive agents.

Nutritional Therapies

- Patients with active CD respond to bowel rest, along with total enteral or total parenteral nutrition (TPN). Bowel rest and TPN are as effective as glucocorticoids at inducing remission of active CD but are not effective as maintenance therapy. However UC does not respond to dietary measures.

Anti-tumor Necrosis Factor Antibody

- TNF is an inflammatory cytokine and mediator of intestinal inflammation. Infliximab is a monoclonal antibody against TNF that is extremely effective in CD. Results on the efficacy of infliximab in UC are mixed. Two other anti-TNF-α agents, adalimumab and certolizumab pegol, may be less immunogenic than infliximab and have shown efficacy in the treatment of Crohn's disease.

Surgical Management

- Surgery (total proctocolectomy with ileostomy) is indicated in severe ulcerative colitis associated with toxic megacolon, colonic perforation and massive colonic hemorrhage. In Crohn's disease surgery is indicated in stricture and obstruction unresponsive to medical therapy, massive hemorrhage and refractory fistula.

Q. Describe the etiology, pathology, clinical features, investigations and treatment of ulcerative colitis.

Etiology

- See Crohn's disease.

Pathology

Macroscopic Changes

- UC usually involves only colon and spares small intestine except in a few patients where terminal ileum can also be involved (backwash ileitis).
- Mucosa is erythematous and has a fine granular surface that looks like sandpaper. Mucosal involvement is continuous without skip lesions.
- Rectum is also involved in 95% of cases.
- Inflammatory swollen mucosa gives the appearance of pseudopolyps.
- In severe inflammation, toxic dilatation can occur.
- On healing, the mucosa can return to normal, although there is usually some residual glandular distortion.

Microscopic Changes

- Mucosa shows a chronic inflammatory cell infiltrate in the lamina propria. Crypt abscesses and goblet cell depletion are also seen.

Clinical Features

- The disease can be mild, moderate or severe, and in most patients runs a course of remissions and exacerbations.
- The major symptom in ulcerative colitis is diarrhea with blood and mucus, sometimes accompanied by lower abdominal discomfort. Diarrhea is often nocturnal and/or postprandial.
- General features include malaise, lethargy and anorexia.
- Aphthous ulceration in the mouth is seen.
- When there is proctitis (rectal inflammation) blood mixed with the stool, urgency and tenesmus are seen.

Investigations

Blood Tests

- Anemia is common due to blood loss. ESR, CRP and white cell counts are raised indicating inflammation. Hypoalbuminemia is present in severe disease due to protein loss from intestine.

Stool Examination

- This should be done to exclude infective causes of colitis.

Plain X-ray Abdomen

- To exclude toxic dilatation of colon.

Flexible Sigmoidoscopy and Colonoscopy

- Sigmoidoscopy is enough, initially since total colonoscopy may precipitate toxic megacolon or perforation severe disease. Colonoscopy can be done in mild cases.
- Mucosa is erythematous. In addition, petechiae, exudates, touch friability, and frank hemorrhage may be present.
- Severe cases may have ulcers, profuse bleeding, and copious exudates. Colonic involvement is continuous in ulcerative colitis (skip lesions in Crohn's disease).
- Pseudopolyps may be present.

Barium Enema

- Rarely used in the diagnosis of ulcerative colitis. It may be normal in mild forms of disease.
- It shows ulcers, shortening of the colon, loss of haustrae, narrowing of the lumen, and pseudopolyps. It should be avoided in severely ill patients as it may precipitate ileus with toxic megacolon.

Colonic Biopsy

- Can be used to confirm the diagnosis. It reveals crypt abscesses and chronic changes including branching of crypts, atrophy of glands, and loss of mucin in goblet cells.

Treatment

- See Crohn's disease.

Q. Comparison of ulcerative colitis and Crohn's disease.

Q. Extraintestinal manifestations of inflammatory bowel disease (IBD).

Table 4.21 Comparison of ulcerative colitis and Crohn's disease

	Ulcerative colitis	Crohn's disease
Male:female ratio	Equal	Slightly more common in males
Smoking	May prevent disease	May cause disease
Oral contraceptives	No increased risk	Increased risk
Appendectomy	Protective	Not protective
Gross blood and mucus in stool	Frequent	Occasional
Systemic symptoms	Occasional	Frequent
Pain abdomen	Occasional	Frequent
Abdominal mass	Rare	Yes
Perineal disease	Rare	Frequent
Small intestinal involvement	No	Yes
Stricture of intestine	Occasional	Frequent
Intestinal obstruction	Rare	Frequent
Response to antibiotics	No	Yes
Recurrence after surgery	No	Yes
ANCA-positive	Frequently	Rarely
Rectal sparing	Rarely	Frequently
Skip lesions	No	Yes
Cobblestone appearance	No	Yes

Extraintestinal Manifestations of Inflammatory Bowel Disease (IBD)

Skin manifestations
- Erythema nodosum
- Pyoderma gangrenosum

Rheumatologic
- Arthritis
- Ankylosing spondylitis
- Sacroiliitis

Ocular
- Conjunctivitis
- Anterior uveitis/iritis
- Episcleritis

Hepatobiliary
- Fatty liver
- Cholelithiasis
- Primary sclerosing cholangitis

Urologic
- Nephrolithiasis
- Ureteral obstruction
- Fistulas

Cardiovascular system
- Deep vein thrombosis
- Pulmonary embolism
- Arterial emboli
- Endocarditis
- Myocarditis
- Pericarditis
- Cerebrovascular accidents

Q. Toxic megacolon.

- Toxic megacolon is total or segmental nonobstructive colonic dilatation plus systemic toxicity. It is a potentially lethal complication of inflammatory bowel disease (IBD) or infectious colitis.
- Only colonic dilatation (e.g. Hirschsprung's disease, chronic constipation, intestinal pseudo-obstruction, diffuse gastrointestinal dysmotility) without systemic toxicity is not considered toxic megacolon.

Etiology

Table 4.22 Causes of toxic megacolon

Inflammatory bowel disease
- Ulcerative colitis
- Crohn's disease

Infectious
- *Clostridium difficile* pseudomembranous colitis
- *Salmonella*—typhoid and non-typhoid
- Shigella
- Campylobacter
- Yersinia
- *Entamoeba histolytica*
- Cryptosporidium
- CMV colitis

Other
- Pseudomembranous colitis secondary to methotrexate therapy
- Kaposi's sarcoma

Pathogenesis

- Mucosal inflammation leads to the release of inflammatory mediators and bacterial products, increased inducible nitric oxide synthase, generation of excessive nitric oxide, and colonic dilatation.
- Extension of the mucosal inflammation to the smooth muscle layer paralyzes the colonic smooth muscle, leading to dilatation.
- Precipitating factors of toxic megacolon include hypokalemia, antimotility agents, opiates, anticholinergics, antidepressants, barium enema, and colonoscopy. Discontinuing or rapid tapering of corticosteroids, sulfasalazine, or 5-ASA compounds in IBD may contribute to the development of megacolon.

Pathology

- Marked dilatation of the colon, thinning of the bowel wall, and deep ulcers.
- Acute inflammation in all layers of the colon.

Clinical Features

- Toxic megacolon affects all ages and both sexes.
- Signs and symptoms of acute colitis may precede the onset of acute dilatation.
- Severe bloody diarrhea is the most common presenting symptom, while improvement of diarrhea may herald the onset of megacolon.
- Physical examination reveals a toxic appearing patient with altered sensorium, tachycardia, fever, postural hypotension, lower abdominal distension and tenderness.
- There may be signs of localized or generalized peritonitis.
- Large doses of steroids and analgesics may mask the signs or symptoms of toxic megacolon.

Investigations

- Anemia related to blood loss.
- Leukocytosis.
- Electrolyte disturbances.
- Hypoalbuminemia.
- ESR and CRP are usually increased.
- Plain X-ray abdomen
- Transverse or right colon is commonly affected.
- Descending colon, sigmoid colon and rectum are rarely affected.
- Multiple air-fluid levels in the colon.
- Normal colonic haustral pattern is either absent or severely disturbed.
- Deep mucosal ulcerations may appear as air filled crevices.
- Stool specimens should be sent for culture, microscopic analysis, and *C. difficile* toxin.
- Ultrasonography and computed tomography (CT)
- Limited endoscopy without bowel preparation is useful to diagnose the cause. Only minimal air should be introduced into the colon to avoid worsening ileus or distention and perforation. Full colonoscopy is risky in toxic megacolon. It can lead to perforation.

Treatment

- Initial therapy is medical. However, a surgical consultation should be obtained upon admission, and the patient should be evaluated daily by both the medical and surgical team.

Medical Therapy

- Patients with IBD should be kept nil per oral and a nasogastric tube is inserted to decompress the gastrointestinal tract. Enteral feeding is begun as soon as the patient shows signs of improvement.
- Anemia, dehydration, and electrolyte imbalances should be treated aggressively.
- All antimotility agents, opiates, and anticholinergics should be discontinued as they aggravate ileus.
- Intravenous H_2 blockers or proton pump inhibitors should be given to prevent gastric stress ulcers.
- Broad-spectrum antibiotics are given to reduce septic complications and to prevent possible peritonitis in case of perforation (third-generation cephalosporin plus metronidazole).
- Intravenous corticosteroids (hydrocortisone 100 mg or equivalent every six to eight hours or by continuous infusion) should be given to all patients for the treatment of underlying ulcerative colitis or Crohn's disease. Steroids do not increase the risk of perforation. Steroids are not used in toxic megacolon due to *C. difficile* colitis or infective colitis.
- If toxic megacolon is due to severe *C. difficile* colitis (antibiotic induced), the first step is to stop the offending antibiotic, followed by oral vancomycin via a nasogastric tube. Intravenous vancomycin has no effect on *C. difficile* colitis since the antibiotic is not excreted into the colon. If there is response to vancomycin intravenous metronidazole may be added at a dose of 500 mg every eight hours.

Surgical Therapy

- Perforation, massive hemorrhage, increasing transfusion requirements, worsening signs of toxicity, and progression of colonic dilatation are absolute indications for surgery.
- Subtotal colectomy with end-ileostomy is the procedure of choice for urgent or emergent surgery.

Q. Discuss the etiology, clinical features, investigations, and management of pseudomembranous colitis (antibiotic-associated colitis).

Etiology

- Pseudomembranous colitis is due to overgrowth of *Clostridium difficile* and toxin production after prolonged broad-spectrum antibiotic therapy.
- Commonly implicated antibiotics are:
  - Ampicillin
  - Clindamycin
  - Tetracycline
  - Third-generation cephalosporins
  - Fluoroquinolones

Pathogenesis

- *C. difficile* is an anaerobic bacterium which colonizes the colon of 3% of healthy adults. It is acquired by fecal-oral transmission. It is readily transmitted from patient to patient by hospital personnel.
- Antibiotics disrupt the normal bowel flora and allow *C. difficile* to flourish.
- After multiplication, it produces two toxins; toxin A and toxin B. Both toxins possess cytotoxic activity and can damage the colon. Both toxins adhere to receptors on the human colonocyte brush border, and cause necrosis and shedding of these cells into the lumen. Both the toxins cause an acute inflammatory diarrhea with massive infiltration of the intestinal mucosa with neutrophils and monocytes.
- Shedding of colonic epithelial cells produces shallow ulcers. Serum proteins, mucus, and inflammatory cells flow outward from the ulcer, creating a pseudomembrane.

Pathology

- Rectum and colon show a yellow or off white membrane adherent to the eroded mucosa (pseudomembrane). Pseudomembranes are patchily distributed.
- There is edema and hyperemia of the full thickness of the bowel wall.

Clinical Features

- Symptoms usually begin during or shortly after antibiotic therapy but may be delayed for up to 2 months.
- Most patients report mild to moderate greenish, foul-smelling watery diarrhea with lower abdominal cramps. With more serious illness, there is abdominal pain and profuse watery diarrhea with up to 30 stools per day. The stools may have mucus but seldom gross blood.
- Physical examination is normal or reveals left lower quadrant tenderness. There may be fever up to 40°C.
- Rarely fulminant colitis with serious complications, such as perforation, prolonged ileus, toxic megacolon, and death can occur.

Investigations

Stool Studies

- Demonstration of *C. difficile* toxins in the stool by cytotoxicity assay (toxin B) or rapid enzyme immunoassays (EIA) for toxins A and B.
- Culture for *C. difficile* is sensitive, but slower (2–3 days), more costly, and less specific than toxin assays, and not used in most clinical settings.
- Fecal leukocytes are present in only 50% of patients with colitis.

Flexible Sigmoidoscopy

- Reveals typical pseudomembranes.

Plain X-ray Abdomen

- To look for evidence of toxic dilation or megacolon but are of no value in mild disease.

Abdominal CT Scan

- Useful in detecting colonic edema, and evaluation of possible complications.

Treatment

- Offending antibiotic should be discontinued. This alone may lead to resolution of symptoms in mild cases.
- If diarrhea is severe, the drug of choice is oral vancomycin, 125 mg orally four times daily due to faster symptom resolution and fewer treatment failures than metronidazole. Vancomycin is not absorbed and acts directly at the infection site. Intravenous vancomycin should not be used as it is not effective. Oral or intravenous metronidazole 500 mg three times daily is an alternative. In fulminant cases, both vancomycin and metronidazole can be combined.
- Fidaxomicin is a new macrolide approved for the treatment of *C. difficile* associated diarrhea. This agent has a narrower antimicrobial spectrum and alters the gut microflora less than do metronidazole and vancomycin.
- Probiotics such as *Saccharomyces boulardii*, and lactobacillus may help in controlling the disease and also prevent relapses.
- Total colectomy may be required in patients with toxic megacolon, perforation, sepsis, or hemorrhage.

Q. Discuss the etiology, clinical features, investigations and management of mesenteric ischemia.

Or

Q. Discuss the etiology, clinical features, investigations and management of ischemic colitis.

- Mesenteric ischemia is caused by a reduction in intestinal blood flow. It can be acute or chronic, involve small or large bowel.
- It is a serious condition and can lead to sepsis, bowel infarction, and death.
- Ischemic colitis is the most frequent form of mesenteric ischemia, affecting mostly the elderly.

Etiology of Mesenteric Ischemia

- Embolic occlusion (emboli arise from heart or aorta)
- Thrombotic occlusion (due to atherosclerosis)
- Hypotension (myocardial infarction, heart failure, arrhythmias or sudden blood loss)
- Vasculitis
- Venous occlusion
- Strangulated hernia
- Colon volvulus

Clinical Features

Small Bowel Ischemia

- It is due to occlusion of superior mesenteric artery.
- Pathological changes may range from mild ischemia to transmural hemorrhagic necrosis and gangrene.
- Sudden onset abdominal pain with minimal physical signs.
- Abdomen may be distended with diminished bowel sounds.
- Signs of peritonitis may be present.
- Patients may have evidence of cardiac disease and arrhythmia responsible for emboli.

Large Bowel Ischemia (Ischemic Colitis)

- The splenic flexure and descending colon are prone for ischemic injury since they have little collateral circulation. Ischemic injury can range from transient colitis to gangrene and fulminant pancolitis.
- Patient is usually elderly
- Sudden onset of cramping left-sided lower abdominal pain and rectal bleeding.
- Symptoms usually resolve over 24–48 hours and healing occurs within 2 weeks.
- Some have a residual fibrous stricture or segmental colitis.
- A minority develop gangrene and peritonitis.

Investigations

- Leucocytosis, metabolic acidosis, and high amylase levels.
- Plain X-ray abdomen shows 'thumb-printing' due to mucosal edema.
- Ultrasound abdomen
- CT abdomen
- Mesenteric or CT angiography shows occluded or narrowed mesenteric artery.
- Investigations for underlying prothrombotic disorders.
- Colonoscopy and barium enema in ischemic colitis.

Treatment

- Patient is kept NPO.
- IV fluids and electrolytes.
- Intravenous antibiotic therapy (ciprofloxacin and metrinidazole)
- Embolectomy and vascular reconstruction if possible
- Thrombolysis may sometimes be effective in patients at high surgical risk.
- Anticoagulation in mesenteric vein thrombosis.
- Laparotomy and resection of the involved segment with end to end anastomosis is required in patients with bowel gangrene and signs of peritonitis.
- Small bowel transplantation can be considered in selected patients.

Q. Discuss the etiology, clinical features, investigations and management of irritable bowel syndrome (IBS).

- Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits in the absence of any organic cause.
- Organic causes should be ruled out before making a diagnosis of IBS.

Etiology

- Hereditary and environmental factors.
- Abnormal gastrointestinal motility in the form of exaggerated gastrocolic reflex, altered gastric emptying, increased small bowel contractions and increased small intestinal transit.
- Visceral hypersensitivity.

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- Neurotransmitters such as serotonin may be an important factor. It stimulates intestinal secretion and peristalsis in addition to visceral pain receptors via 5-HT3 and 5-HT4 pathways.
- *Microscopic inflammation*: Detailed immunohistologic investigation has revealed mucosal immune system activation in a subset of patients with irritable bowel syndrome (mostly those with the diarrhea predominant type).
- *Psychologic disturbances*: Many patients with IBS have increased anxiety, depression, phobias, and somatization.
- Certain foods may precipitate an attack, e.g. excess coffee.

Clinical Features

- IBS is common in young people. It is 3 times more common in women.

Rome III Criteria For the Diagnosis of IBS

- Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following:
  1. Relieved by defecation
  2. Onset associated with changes in stool frequency
  3. Onset associated with changes in stool form
- Four subtypes of IBS have been recognized:
  1. Constipation predominant
  2. Diarrhea predominant
  3. Mixed
  4. Alternating diarrhea and constipation. The usefulness of this classification is debatable because the symptoms can change from one type to another in a given patient.
- Abdominal pain in IBS is highly variable in intensity and location. It is frequently episodic and crampy, but may be dull aching also. Pain may be mild or it may interfere with daily activities. Abdominal pain is mainly present during daytime hence sleep disturbance is rare. Pain is often exacerbated by eating or emotional stress and relieved by passage of flatus or stools.
- Alteration in bowel habits usually begins in adult life. The most common pattern is constipation alternating with diarrhea, usually with one of these symptoms predominating. Diarrhea in IBS usually consists of small volumes of loose stools. Nocturnal diarrhea does not occur in IBS. Bleeding, malabsorption and weight loss does not occur in IBS.
- Patients with IBS also complain of increased belching or flatulence. Many patients also complain of dyspepsia, heartburn, nausea, and vomiting.

Differential Diagnoses

- Anxiety disorders
- Bacterial overgrowth syndrome
- Malabsorption syndromes (such as celiac sprue)
- Gastroenteritis
- Giardiasis
- Hypercalcemia
- Hyperthyroidism
- Inflammatory bowel disease
- Colon cancer

Investigations

- Since IBS is a diagnosis of exclusion, certain investigations should be done routinely to exclude other diseases with similar presentation.
- Complete blood count.
- Stool examination—to look for ova, cysts and occult blood.
- Colonoscopy—in those older than 50 years to rule out carcinoma colon.
- Hydrogen breath test—if the main symptoms are diarrhea and increased gas to rule out malabsorption.
- Upper GI scopy—if the patient has prominent dyspepsia.
- Ultrasound abdomen.

Treatment

Patient Counseling and Dietary Alterations

- Patients should be reassured and functional nature of the disorder explained. Foods which aggravate symptoms (such as coffee, disaccharides, legumes, and cabbage) should be avoided.

Stool-Bulking Agents

- High-fiber diets and bulking agents, such as bran or hydrophilic colloid, are helpful in treating IBS. Dietary fiber has multiple effects on colonic physiology. Because of their hydrophilic properties, stool-bulking agents bind water and thus prevent both excessive hydration and dehydration of stool. Hence these agents can reduce both diarrhea and constipation in IBS patients.

Antispasmodics

- Anticholinergic drugs may provide temporary relief for symptoms such as painful cramps related to intestinal spasm.

Antidiarrheal Agents

- Peripherally acting opiate-based agents are the initial therapy of choice for diarrhea-predominant IBS.
- Diphenoxylate (lomotil), 2.5 to 5 mg every 4 to 6 h, can be prescribed. Codeine is also helpful. These agents should be used only temporarily and should be replaced gradually with high-fiber diet.

Antidepressant Drugs

- Tricyclic antidepressants (amitryptyline, imipramine, desipramine) slow jejunal migrating motor complex transit propagation and delays orocecal and whole-gut transit. They improve diarrhea, pain, and depression.
- The selective serotonin reuptake inhibitor (SSRI) paroxetine accelerates orocecal transit, and may be useful in constipation-predominant patients.
- The SSRI citalopram blunts perception of rectal distention and reduces abdominal pain.

Serotonin Receptor Agonists and Antagonists

- A $5HT_3$ receptor antagonist alosetron reduces abdominal discomfort and improves stool frequency, consistency, and urgency in nonconstipated IBS patients. However a major side effect ischemic colitis was observed due to this drug and hence this drug has been withdrawn from the market. A newer $5HT_3$ receptor antagonist, cilansetron, has been shown to improve abdominal pain and diarrhea as alosetron.
- $5HT_4$ receptor agonists stimulate peristalsis. Example, tegaserod reduces abdominal discomfort and improvements in constipation and bloating in IBS patients with constipation. Tegaserod has been approved for the treatment of constipation-predominant IBS.

Lubiprostone

- This agent activates chloride channels in the small intestine. As a result, chloride ions are secreted and sodium and water passively diffuse into the lumen to maintain isotonicity. It is useful in constipation predominant IBS.

Q. Enumerate the causes of acute abdomen. What are the clinical features of acute abdomen? How do you investigate and manage a case of acute abdomen?

Causes of Acute Abdomen

Table 4.23 Causes of acute abdomen

Surgical causes	Medical causes
• Acute appendicitis	• Acute pyelonephritis
• Renal colic	• Diabetic ketoacidosis
• Gynecological disorders (torsion of ovarian cyst)	• Acute intermittent porphyria
• Intestinal obstruction	• Lead poisoning
• Urinary tract infection	• Hemophilia and other bleeding disorders
• Gallbladder disease	• Henoch-Schönlein purpura
• Perforated ulcer	• Sickle cell crisis
• Diverticular disease	• Polycythemia vera
	• Embolic phenomenon

Clinical Features of Acute Abdomen

History

- *Complaints*: Acute abdomen usually presents with pain abdomen. Find out the exact location and nature of pain. In general, the pain of an acute abdomen can either be constant (due to inflammation) or colicky because of a blocked hollow organ.
- A sudden onset of pain suggests a perforation (e.g. of a duodenal ulcer), a rupture (e.g. of an aneurysm or ectopic pregnancy), torsion (e.g. of an ovarian cyst), or acute pancreatitis.
- Vomiting is usually present in any acute abdomen but, if persistent, suggests intestinal obstruction. The character of the vomitus should be asked—does it contain blood, bile or small bowel contents.
- Absolute constipation and abdominal distension may be present in intestinal obstruction.
- *Past history*: Enquire about any previous operations, gynecological problems and any concurrent medical condition.

General Examination

- The general condition of the patient should be assessed.
- Most acute abdomen patients look acutely ill.
- Fever suggests an acute infectious process.
- Note pulse rate, respiratory rate, blood pressure and state of hydration. Large volumes of fluid may be lost from the vascular compartment into the peritoneal cavity or into the lumen of the bowel, giving rise to hypovolemia, i.e. a pale cold skin, a weak rapid pulse and hypotension.

The Abdomen

- ***Inspection***: Note the presence of scars, distension or masses.
- ***Palpation***: Tenderness, rebound tenderness, presence or absence of guarding should be noted. Guarding indicates peritonitis. Guarding can be localized or generalized.
- ***Bowel sounds***: Increased bowel sounds indicate intestinal obstruction. Absent bowel sounds suggest peritonitis.
- Other systems should be examined to rule out any concurrent disease.

Investigations

- ***Blood count***: White cell count is raised in inflammatory conditions.
- ***Serum amylase and lipase***: High levels (more than five times normal) indicate acute pancreatitis.
- ***Urine pregnancy test***: Should be done in women of child bearing age to rule out ectopic pregnancy and its rupture.

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- *X-ray erect abdomen*: Air under the diaphragm may be seen in abdominal viscus perforation. Multiple air fluid levels are seen in peritonitis and intestinal obstruction.
- *Ultrasound*: This is useful in the diagnosis of acute cholangitis, cholecystitis and aortic aneurysm, acute pancreatitis and acute appendicitis. It can detect renal and ureteric stones and ruptured ectopic gestation.
- *CT scan*: It is more accurate than ultrasound in most acute emergencies.
- *Laparoscopy*: This has gained increasing importance as a diagnostic tool prior to proceeding with surgery. In addition, therapeutic maneuvers, such as appendicectomy, can be performed.

Treatment of Acute Abdomen

- Acute abdomen is a surgical emergency.
- Initial treatment involves keeping the patient nil per oral and continous nasogastric aspiration of stomach contents through a Ryle's tube.
- Hydration should be maintained by intravenous fluids.
- Empirical antibiotis (cephalosporins plus metroinidazole or tinidazole intravenously) should be started pending the identification of cause.
- Once the cause is identified, treatment should be directed towards that.
- Most cases of acute abdomen require surgery for the underlying cause (e.g. acute appendicitis, perforation of peptic ulcer, etc.).

Q. Describe the etiology, clinical features and management of acute peritonitis.

- Peritonitis is an inflammation of the peritoneum.
- It may be acute or chronic, localized or diffuse, infectious or due to aseptic inflammation.
- Acute peritonitis is most often infectious and is usually related to a perforated viscus.

Etiology

Table 4.24 Causes of acute peritonitis

Perforation of bowel	*Perforations or leaking of other organs*
• Penetrating trauma	• Pancreatitis
• Appendicitis	• Cholecystitis
• Diverticulitis	• Salpingitis
• Peptic ulcer	*Iatrogenic*
• Inflammatory bowel disease	• Peritoneal dialysis
• Endoscopic perforation	• After ascitic fluid tapping
• Ischemia	• Postoperative
• Strangulated hernias	

Localized Peritonitis

- This is seen with acute inflammatory conditions of the gastrointestinal tract (e.g. acute appendicitis, acute cholecystitis). There is local pain and tenderness. The treatment is for the underlying disease.

Generalized Peritonitis

- This is a surgical emergency and is usually due to perforation of a hollow viscus (e.g. perforated appendix, perforated peptic ulcer).
- In case of perforated peptic ulcer, acid contents leak into peritoneal cavity and cause chemical peritonitis which gets infected later with bacteria.
- E. *coli* and *bacteroides* are the most common organisms responsible for peritonitis since these are present in the intestine.
- The peritoneal cavity becomes acutely inflamed, with production of an inflammatory exudate that spreads throughout the peritoneum, leading to intestinal dilatation and paralytic ileus.

Clinical Features

- The cardinal manifestations of peritonitis are acute abdominal pain and tenderness, usually with fever.
- The location of the pain depends on the underlying cause and whether the inflammation is localized or generalized. In case of localized peritonitis physical findings are limited to the area of inflammation. Generalized peritonitis is associated with diffuse abdominal tenderness and rebound tenderness.
- Rigidity of the abdominal wall is common in both localized and generalized peritonitis.
- Bowel sounds are usually absent due to paralytic ileus.
- Tachycardia, hypotension, and signs of dehydration are common.

Investigations

- Leukocytosis and acidosis.
- Elevated serum amylase and lipase levels may detect pancreatitis.
- Plain abdominal X-ray shows dilated and edematous bowel loops with air fluid levels. Gas under the diaphragm may be seen in case of a perforated viscus.
- CT and/or ultrasonography can identify the cause of acute abdomen and the presence of free fluid or an abscess.
- If ascites is present, fluid should be aspirated and sent for cell count cell type, protein, lactate dehydrogenase levels, Gram's stain and culture (>250 neutrophils/μl is usual in peritonitis).

Treatment

- Patient should be hydrated well with IV fluids.
- Continous nasogastric aspiration should be done in view of paralytic ileus.
- Empirical antibiotis (cephalosporins plus metroinidazole or tinidazole intravenously) should be started.
- Treatment of peritonitis is always surgical. Usually laparotomy is required.
- Surgery has a two-fold objective; peritoneal lavage of the abdominal cavity and specific treatment of the underlying condition.

Q. Discuss the causes, clinical features, investigations and management of intestinal obstruction.

- Intestinal obstruction may be mechanical or non-mechanical (e.g. paralytic ileus).

Causes of Obstruction

Table 4.25 Causes of intestinal obstruction

Mechanical obstruction	Non-mechanical (pseudo-obstruction)
• Adhesive bands • Obstructed hernia • Diverticulitis • Intestinal neoplasms • Regional enteritis • Gallstone obstruction • Intussusception • Volvulus	• *Adynamic ileus*—peritonitis, retroperitoneal, lower-lobe pneumonia, electrolyte disturbances (hypokalemia) • *Spastic ileus, or dynamic ileus*—results from prolonged contraction of the intestine. Seen in heavy metal poisoning, uremia, porphyria, and extensive intestinal ulcerations.

Pathophysiology

- Distension of the intestine is caused by the accumulation of gas and fluid proximal to and within the obstructed segment.
- Most of the air consists of swallowed air. Fluid accumulation is due to ingested fluid, swallowed saliva, gastric juice, and biliary and pancreatic secretions. Fluid from the body may also move into the lumen causing further accumulation of fluid. This may lead to sequestration of large volumes of fluid in the lumen leading to dehydration, hypotension, shock and renal failure.
- Blood supply to the obstructed segment of intestine may get compromised (e.g. in obstructive hernia) and lead to gangrene of intestine and blood loss into the lumen.
- Bacteria may get into the peritoneum through the gangrenous segment leading to peritonitis.
- Massive abdominal distension may compromise breathing and cause inferior vena cava compression.

Clinical Features

- Patient presents with colicky abdominal pain, vomiting and constipation.
- Examination of the abdomen reveals distension with increased bowel sounds.
- Pulse is rapid and there may be dehydration and signs of shock.
- Tenderness of abdomen suggests strangulation or peritonitis, and urgent surgery is necessary.
- Examination of the hernial orifices and rectum must be performed.

Investigations

- Plain X-ray of the abdomen (erect view) shows distended bowel loops with air fluid levels.
- Ultrasound abdomen and CT can identify the cause of obstruction.

Management

- Initial management is by resuscitation with intravenous fluids (mainly isotonic saline with potassium) and continuous nasogastric aspiration through a Ryle's tube. Many cases will settle on conservative management.
- Exploratory laparotomy may be required in serious cases not responding to conservative therapy. If the bowel is gangrenous, that segment has to be resected and end to end anastomosis done.

Q. Probiotics.

- Probiotics are microorganisms that have beneficial properties for the host. Examples are Lactobacillus, Bifidobacterium, *Clostridium butyricum, Streptococcus salivarius,* and *Saccharomyces boulardii.*

Mechanisms of Benefit

- Suppression of growth or invasion by pathogenic bacteria.
- Improvement of intestinal barrier function.
- Modulation of the immune system.

Potential Uses

- Ulcerative colitis
- Crohn's disease
- Antibiotic associated diarrhea
- Infectious diarrhea
- Irritable bowel syndrome
- Lactose intolerance
- Hepatic encephalopathy
- Allergy

Q. Prebiotics.

- Prebiotics are dietary substances that induce the growth and/or activity of beneficial microorganisms (e.g. bacteria and fungi) that contribute to the well-being of their host.
- In diet, prebiotics are typically non-digestible fiber compounds that pass undigested through the upper part of the gastrointestinal tract and stimulate the growth and/or activity of advantageous bacteria that colonize the large bowel by acting as substrate for them.
- Commonly known prebiotics are: oligofructose, inulin, galacto-oligosaccharides, lactulose, breast milk oligosaccharides.

Sources of Prebiotics

- Chicory root is the richest natural source. Other dietary sources are beans, raw oats, unrefined wheat, unrefined barley, onion, garlic and raw banana.

Effects of Prebiotics

- Reduce exogenous and endogenous intestinal infection
- Improved bowel habit
- Suppress IBD inflammation
- Immunomodulation (anti-inflammatory)
- Controlled serum lipids and cholesterol.

Q. Carcinoid syndrome.

- Carcinoid tumors are neoplastic proliferation of enterochromaffin cells.
- Carcinoid tumors can be found in GIT, bronchi, thyroid, ovary and testes.
- In GIT, the most common site is ileum and appendix.
- These tumors are less aggressive than carcinomas and their growth is usually slow. They can spread locally and also metastasize to other organs especially liver.
- Carcinoid syndrome refers to the systemic symptoms produced by secretory products of carcinoid tumors. The secretory products produced by the primary tumor are metabolized in the liver and hence, do not reach the systemic circulation. However, when there are liver metastases, secretory products from these metastases reach systemic circulation and produce symptoms. Therefore carcinoid syndrome is seen only when there are liver metastases.
- These tumors follow the so-called rule of one-third, which is as follows:
  - One-third of these tumors are multiple
  - One-third of those in the gastrointestinal (GI) tract are located in the small bowel
  - One-third of patients have a second malignancy
  - One-third of these tumors metastasize.

Secretory Products of Carcinoid Tumor

Table 4.26 Secretory products of carcinoid tumor

• Serotonin • Histamine • Norepinephrine • Dopamine • Bradykinins • Motilin	• Adrenocorticotrophic hormone (ACTH) • Corticotrophin releasing factor • Prostaglandins somatostatin • Vasoactive intestinal peptide • Gastrin

Clinical Features

- Carcinoids occur most frequently in patients aged 50–70 years.
- Episodic cutaneous flushing is the clinical hallmark of the carcinoid syndrome, and occurs in most of patients. It occurs in the face, neck, upper chest and lasts from 30 seconds to 30 minutes. There may be associated lacrimation, periorbital edema, tachycardia and hypotension.
- Venous telangiectasias are purplish vascular lesions seen on the face, and occur due to prolonged vasodilatation.
- Secretory diarrhea occurs in most patients. Stools are watery and non-bloody, and may be accompanied by abdominal cramping.
- Wheezing and dyspnea due to bronchospasm often during flushing episodes.
- Cardiac valvular lesions: right sided valves (tricuspid regurgitation and pulmonary stenosis) are most often affected, because inactivation of humoral substances by the lung protects the left heart.
- Diversion of tryptophan for synthesis of serotonin can result in the development of pellagra. Normally niacin is produced from tryptophan.
- Hepatomegaly due to hepatic metastases, intestinal obstruction and bleeding from intestinal tumors.
- Other features include increased incidence of peptic ulcer, muscle wasting due to poor protein synthesis and ureteral obstruction due to retroperitoneal fibrosis.

Investigations

- Increased urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) in 24-hour collection (more than 9 mg). 5-HIAA is the end product of serotonin metabolism.
- Serotonin level in blood and platelets is high.
- Chest X-ray, CT scan, barium and endoscopic studies are used to localize the tumor.
- Scintigraphy with indium-111 diethylenetriamine penta acetic acid (DTPA) octreotide (In-111 DTPA Octr), or OctreoScan, localizes the carcinoid tumor with high sensitivity and specificity.

- Laparotomy and biopsy of the leison can be attempted in selected cases.

Treatment

- The treatment of a carcinoid tumor without liver metastases is surgical resection.
- The treatment of carcinoid tumor with liver metastases (carcinoid syndrome) is palliative. However, primary tumour and hepatic metastases can be excised as it decreases the tumor burden and improves the symptoms. Hepatic artery embolisation can decrease the size of hepatic metastases. Octreotide 200 μg 8-hourly by subcutaneous injection is used to reduce release of secretory products by tumor. Cytotoxic chemotherapy has only a limited role.
- Symptomatic treatment: Bronchodilators for wheeze, loperamide and serotonin-receptor antagonists (cyproheptadine, ondansetron) to control diarrhea.
- Avoidance of conditions and diets precipitating flushing and diarrhea.
- Supplementation of food with niacin to prevent pellagra.

Q. Zollinger-Ellison syndrome (gastrinoma).

- Zollinger-Ellison syndrome is caused by gastrin-secreting gut neuroendocrine tumors (gastrinomas), which result in hypergastrinemia and increased acid secretion.
- Gastrinomas may arise in the pancreas, duodenum or lymph nodes. Most of them are found within the "gastrinoma triangle" bounded by porta hepatis, neck of the pancreas, and third part of duodenum.
- Most gastrinomas are solitary or multifocal nodules that are potentially resectable. Over two-thirds of gastrinomas are malignant, and one-third would have already metastasized to the liver at initial presentation. Multifocal gastrinomas are associated with MEN 1 syndrome.

Clinical Features

- Abdominal pain occurs due to peptic ulcers. Over 90% of patients with Zollinger-Ellison syndrome develop peptic ulcers. Ulcer is usually single and found in the duodenum, but there can be multiple ulcers. These ulcers may be refractory to standard treatment, big (>2 cm), and my reccur.
- Symptoms of gastroesophageal reflux.
- Diarrhea and weight loss occur in one-third of patients due to direct intestinal mucosal injury and pancreatic enzyme inactivation by acid, leading to maldigestion, and malabsorption.

Investigations

- Upper GI endoscopy: to look for duodenal ulcerations and hypertrophy of gastric folds.
- *Increased fasting serum gastrin concentration (>150 pg/mL)*: H_2-blocker should be withheld for 24 hours and proton pump inhibitors for 6 days before measuring gastrin levels.
- Measurement of gastric pH: Most patients have a basal acid output of over 15 mEq/h. A gastric pH of >3.0 implies hypochlorhydria and excludes gastrinoma.
- Secretin stimulation test: Useful to distinguish Zollinger-Ellison syndrome from other causes of hypergastrinemia. Intravenous secretin produces arise in serum gastrin within minutes in patients with gastrinoma.
- High serum calcium level suggests hyperparathyroidism and MEN 1 syndrome.
- Serum parathyroid hormone (PTH), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and growth hormone (GH) level should be obtained to exclude MEN 1.
- Imaging studies are used to locate the site of primary tumor and to identify metastases. Gastrinomas express somatostatin receptors that bind radiolabeled octreotide. Somatostatin receptor scintigraphy (SRS) with single photon emission computed tomography (SPECT) can identify the site of gastrinomas. Endoscopic ultrasonography (EUS) may be useful to detect small gastrinomas in the duodenal wall, pancreas, or peripancreatic lymph nodes. CT and MRI scans may be helpful to identify liver metastases and primary lesions, but less sensitive than SPECT.

Treatment

- Localized disease is treated with surgical resection.
- In patients with liver metastases, initial therapy should be directed at controlling hypersecretion. Oral proton pump inhibitors (omeprazole, esomeprazole, rabeprazole, pantoprazole, or lansoprazole) are used to decrease the acid secretion. Surgical resection or cryoablation can be tried for single metastases. Other options for liver metastases include somatostatin analogues, interferon alpha, cytotoxic chemotherapy, and hepatic arterial chemoembolization.

Q. Gardner's syndrome (familial adenomatous polyposis).

- This is an uncommon autosomal dominant disorder characterized by multiple adenomatous polyps throughout the colon. Hundreds to thousands of adenomatous colonic polyps will develop by age 15. Most will develop colorectal cancer by the age of 50 years.

- It results from germline mutation of the APC gene on the long arm of chromosome 5 followed by acquired mutation of the remaining allele.
- Many extra-intestinal features are also seen in FAP which include; subcutaneous epidermoid cysts, osteomas, dental abnormalities, retinal abnormalities, desmoid tumors, and lipomas.
- Investigations include colonoscopy and genetic testing. All first-degree relatives of the affected patients should also undergo testing. In families with known FAP, at-risk family members should undergo direct mutation testing at 13–14 years of age.
- Affected individuals should undergo colectomy (total proctocolectomy with ileal pouch-anal anastomosis). This will prevent the transformation of polyps into adenocarcinoma.

Q. Peutz-Jeghers syndrome.

- This is characterised by multiple hamartomatous polyps in the small intestine and colon, as well as melanin pigmentation of the lips, mouth and digits.
- The disorder is caused by a mutation on chromosome 19p.
- Most cases are asymptomatic. However, chronic bleeding, anemia or intussusception may be seen. Malignant potential of polyps is low though there is a small risk of adenocarcinoma.
- Management involves surveillance of polyps with colonoscopy and biopsy every 1 to 3 years.

Q. Discuss the etiology, clinical features, investigations and management of acute pancreatitis. What are the complications of acute pancreatitis?

- Acute pancreatitis is an inflammatory condition of the pancreas characterized by abdominal pain and elevated levels of pancreatic enzymes in the blood.

Etiology

Table 4.27 Causes of acute pancreatitis

Common causes	Rare causes
• Gallstones • Alcohol • Post-ERCP • Idiopathic	• Post-surgical (abdominal, cardio-pulmonary bypass) • Trauma (blunt or penetrating abdominal injury) • Drugs (azathioprine, thiazides, sulphasalazine, valproate) • Metabolic (hypercalcemia, hypertriglyceridemia) • Pancreas divisum • Vascular (ischemia, atheroembolism, vasculitis) • Infections (mumps, coxsackievirus, HIV, leptospira, ascaris) • Cystic fibrosis • Toxins (methanol, scorpion venom, organophosphates) • Renal failure • Organ transplantation (kidney, liver) • Severe hypothermia

Pathophysiology

- Damage to pancreas by any of the above causes leads to premature activation of zymogen granules, releasing proteases which digest the pancreas and surrounding tissue.
- Pancreas becomes swollen. In severe cases there may be necrosis and hemorrhage.
- Pancreas has a poorly developed capsule, and adjacent structures, including the common bile duct, duodenum, splenic vein and transverse colon, are commonly involved.
- Both the endocrine and exocrine function of the pancreas is altered during an attack of acute pancreatitis which will return to normal if the attack is mild. However, permanent exocrine and endocrine insufficiency may develop in severe pancreatitis (necrotizing pancreatitis).

Clinical Features

Symptoms

- Abdominal pain: Severe, constant upper abdominal pain which radiates to the back. Pain is sudden in onset and gradually increases in severity. Pain decreases if patient sits up and leans forward and increases on lying down.
- Nausea and vomiting.
- Anorexia.

Signs

- Fever (low-grade).
- Tachycardia.
- Tachypnea (due to pleural effusion, inflammation of lungs, or atelectasis).
- Jaundice due to compression of common bile duct.
- Epigastric tenderness.
- Guarding and rebound tenderness in severe cases.
- Bluish discoloration of the flanks (Grey Turner's sign) or the periumbilical region (Cullen's sign) are features of severe pancreatitis with hemorrhage.
- Absent bowel sounds due to paralytic ileus.
- Hypotension and shock in severe cases.
- Erythematous skin nodules due to focal subcutaneous fat necrosis.

- Ischemic injury to retina seen on fundus examination (Purtscher retinopathy).

Investigations

Serum Amylase

- This is elevated in acute pancreatitis for three to five days. It is rapidly cleared by kidneys. Hence, levels may be normal if measured after 3–5 days. In this situation the diagnosis can be made by elevated urinary amylase: creatinine ratio. A persistently elevated serum amylase concentration suggests pseudocyst formation. High amylase levels are also found in pancreatic ascites and pleural effusion. Serum amylase concentration has no prognostic value.
- Elevated amylase is not specific to pancreatitis. High serum amylase levels can also occur in mesenteric ischemia, perforated peptic ulcer, ruptured ovarian cyst, renal failure, DKA, and parotitis.

Serum Lipase

- This is more specific than that of amylase in diagnosing pancreatitis.
- Lipase takes longer time to clear from the blood. Hence, it is helpful to make a diagnosis of pancreatitis even if the patient presents late.

Ultrasound Abdomen

- Shows swollen pancreas. It is also useful to pick up gallstones, biliary obstruction or pseudocyst formation.

CT Scan Abdomen

- This is the most important imaging test for the diagnosis of acute pancreatitis and its local complications. Patients who do not improve with initial conservative therapy or who are suspected of having complications should undergo CT scan of the abdomen.
- MRI is an alternative to CT especially if contrast cannot be used due to renal failure.

Plain X-ray Abdomen and Chest

- To exclude other causes of acute abdominal pain (e.g. gas under diaphragm in perforation).
- Calcification in pancreas in chronic pancreatitis.
- Multiple air fluid levels due to paralytic ileus.
- Chest X-ray may show pleural effusion and signs of ARDS.

Other Blood Investigations

- Blood glucose, total leukocyte count, platelet count, ESR, CRP, blood urea, creatinine, calcium and other electrolytes, triglycerides, arterial blood gases.

Assessment of Severity of Acute Pancreatitis

Ranson Criteria to Predict Severity of Acute Pancreatitis

Table 4.28 Ranson criteria

On admission	First 48 hours
• Age >55 • White blood cell count >16,000/mm^3 • Blood glucose >200 mg/dl • Lactate dehydrogenase >350 U/L • Aspartate aminotransferase (AST) >250 U/L	• Hematocrit fall by >10% • Blood urea increase by 5 mg/dl despite fluids • Serum calcium <8 mg/dl • pO_2 <60 mmHg • Base deficit >4 mEq/L • Fluid sequestation >6 litres

- Each of the above parameter counts for 1 point toward the score. A Ranson score of 0–2 has a minimal mortality. A Ranson score of 3–5 has a 10–20% mortality rate, and the patient should be admitted to the intensive care unit (ICU). A Ranson score higher than 5 after 48 hours has a mortality of more than 50% and is associated with more systemic complications.

Complications of Acute Pancreatitis

Table 4.29 Complications of acute pancreatitis

Local	Systemic
• Pancreatic necrosis • Abscess formation • Pseudocyst formation • Pancreatic ascites or pleural effusion • Upper gastrointestinal bleeding • Splenic or portal vein thrombosis • Erosion into colon • Duodenal obstruction (compression by pancreatic mass) • Obstructive jaundice (due to compression of common bile duct)	• Systemic inflammatory response syndrome (SIRS) and multiorgan failure • DIC • Renal failure • Hypoxia • Acute respiratory distress syndrome (ARDS) • Hyperglycemia • Fat necrosis • Hypocalcemia (due to sequestration of calcium in fat necrosis) • Hypoalbuminemia (due to increased capillary permeability)

Differential Diagnosis

- Perforated peptic ulcer
- Perforation of any other hollow viscus
- Acute cholecystitis
- Acute intestinal obstruction
- Leaking aortic aneurysm
- Renal colic
- Acute mesenteric ischemia or thrombosis.

Management

- Nothing by mouth.
- Intravenous fluids to maintain intravascular volume.
- Analgesics for abdominal pain. Adequate pain control requires opiates such as meperidine or tramadol.
- Nasogastric aspiration: not routinely necessary. Required if the patient has persistent abdominal pain inspite of analgesics, paralytic ileus, protracted vomiting or intestinal obstruction.
- Admit severe cases in intensive care unit. Monitor pulse, BP, abdominal girth, urine output, blood glucose and calcium levels.
- Prophylactic systemic antibiotics (imipenem or meropenem or ceftazidime) should be given in severe cases to prevent pancreatic infection.
- Proton-pump inhibitors are used to decrease the acid output.
- The role of somatostatin or octreotide infusion is controversial.
- ERCP with endoscopic sphincterotomy and stone extraction is indicated if pancreatitis results from gallstone particularly if jaundice (serum total bilirubin >5 mg/dl) or cholangitis is present.
- Surgery is indicated for complications such as infected pancreatic necrosis, pancreatic abscess, intestinal obstruction, perforation, etc.

Q. Chronic pancreatitis.

- Chronic pancreatitis is a chronic inflammatory disease of pancreas characterised by fibrosis and destruction of exocrine pancreatic tissue.
- Diabetes mellitus occurs in advanced cases because the islets of Langerhans are involved.

Causes of Chronic Pancreatitis

Table 4.30 Causes of chronic pancreatitis

- Chronic alcoholism
- Tropical (India)
- Stenosis of the ampulla of Vater
- Pancreas divisum
- Cystic fibrosis
- Familial
- Autoimmune diseases (Sjögren's syndrome, primary biliary cirrhosis)
- Idiopathic

Clinical Features

- Middle-aged alcoholic men are predominantly affected.
- Pain in the upper abdomen which may be constant or intermittent. It may radiate to back. Pain may be relieved by leaning forward and worsened by food intake.
- Features of malabsorption: diarrhoea, steatorrhea, and weight loss.
- Diabetes develops in advanced cases.
- Physical examination reveals a thin, malnourished patient with epigastric tenderness. Skin pigmentation over the abdomen and back is common due to chronic use of a hot water bottle to relieve the abdominal pain.

Investigations

- Serum amylase and lipase usually normal
- Ultrasound abdomen
- CT (may show atrophy, calcification, ductal stricture or dilatation)
- Abdominal X-ray (may show calcification)
- ERCP accurately demonstrates the anatomy of pancreatic ducts. Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive alternative to ERCP.
- Endoscopic ultrasound
- Tests of pancreatic function: Seceretin/cholecystokinin (CCK) stimulation test, 24-hour faecal fat estimation, oral glucose tolerance test.

Complications of Chronic Pancreatitis

- Pseudocyst
- Pancreatic ascites
- Obstructive jaundice due to stricture of the common bile duct as it passes through the diseased pancreas
- Duodenal stenosis
- Portal or splenic vein thrombosis
- Peptic ulcer

Management

- Stop alcohol intake.
- *Pain relief*: NSAIDs, opiates, celiac ganglion blockade.
- Oral pancreatic enzyme supplements to improve the digestion and absorption of food.
- Patients with severe chronic pain resistant to conservative measures are considered for surgical or endoscopic pancreatic therapy.
- Endoscopic therapy involves dilatation or stenting of pancreatic duct strictures and removal of calculi (mechanical or shock-wave lithotripsy).
- Surgical interventions are partial pancreatic resection preserving the duodenum, total pancreatectomy and pancreatico-jejunostomy.

Q. Discuss the causes and differential diagnosis of acute upper abdominal pain.

Causes of Acute Upper Abdominal Pain

Table 4.31 Causes of acute upper abdominal pain

• Peptic ulcer perforation	• Lower lobe pneumonia
• Acute cholecystitis	• Myocardial infarction
• Biliary colic	• Aortic dissection or rupture
• Acute pancreatitis	• Splenic abscess and infarct

Peptic Ulcer Perforation

- History of recurrent epigastric pain with relation to food and periodicity.
- Pain is severe and penetrating type. Initially it is felt in the epigastrium, but later spreads to whole abdomen due to generalized peritonitis.
- Tachycardia and hypotension are usually present.
- Abdominal examination shows board like rigidity, guarding and absent bowel sounds due to peritonitis. Liver dullness may be absent or reduced due to gas collection below the diaphragm.
- Plain X-ray abdomen in the erect posture may show gas under the diaphragm and multiple air fluid levels.

Acute Cholecystitis

- Pain is mainly in the right hypochondrium. Pain is constant and may also be felt in the right shoulder tip.
- Associated fever, jaundice, nausea and vomiting.
- Tenderness in the right hypochondrium and rigidity. Murphy's sign present (sudden inspiratory arrest due to pain while palapating right hypochondrium).
- Gallbladder may be palpable.
- Blood tests show leukocytosis, raised bilirubin and liver enzymes.
- Plain X-ray abdomen may show gallstones.
- Ultrasound abdomen may show gallstones, gallbladder wall thickening and pericholic fluid collection.
- Cholescintigraphy shows cystic duct obstruction.

Biliary Colic

- Biliary colic is usually due to gallbladder contracting and pressing a stone against the gallbladder outlet or cystic duct opening, leading to increased gallbladder pressure and pain.
- Biliary colic is a misnomer, since the pain is not typically colicky.
- Pain is deep and gnawing type and is occasionally sharp and severe.
- Pain is localized in the right upper quadrant or epigastrium.
- As the gallbladder relaxes, stones often fall back from the cystic duct. As a result, the attack reaches a crescendo over many hours and resolves completely.
- Pain may recur multiple times.

Acute Pancreatitis

- History of precipitating factors like alcohol binge, and gallstones.
- Pain is steady and usually felt in the mid-epigastrium, radiates to back between scapulae. Its onset is rapid, but not as abrupt as that with a perforated viscus.
- Pain of pancreatitis lasts for many days. Pain is accompanied by nausea and vomiting.
- Pain decreases on sitting and leaning forward.
- Cullen's sign and Grey Turner's sign rarely.
- Amylase and lipase are elevated.
- Ultrasound abdomen and CT scan shows swollen pancreas.

Lower Lobe Pneumonia

- Lower lobe pneumonia causes referred pain to upper abdomen probably due to diaphragmatic irritation.
- Pleuritic chest pain may be present in the lower chest.
- Fever, dyspnea and cough with expectoration are usually present.
- Chest examination reveals crepitations and bronchial breath sounds over the affected area.
- Chest X-ray shows pneumonic patch.
- Abdominal pain is occasionally the sole presenting complaint in a patient with lower lobe pneumonia.

Myocardial Infarction

- Risk factors such as old age, hypertension, diabetes, and smoking may be present.
- Pain is felt more in the left side of chest and restrosternal area. It may radiate to left shoulder and left arm.
- There may be associated symptoms such as dypnea, sweating.
- Examination may show bilateral basal crepitations over the lungs, third and fourth heart sound.
- ECG shows evidence of MI such as ST segment elevation and pathological Q waves.
- CK-MB and troponins are elevated.
- Echocardiogram shows akinesia or hypokinesia of the involved myocardium.

Aortic Dissection

- Sudden, severe, tearing pain radiating to the back.
- Predisposing factors may be present such as; hypertension, previous aortic aneurysm, Marfan's syndrome, etc.

- Asymmetric pulses may be present.
- Chest X-ray shows mediastinal and/or aortic widening.
- CT, MRI or aortogram can confirm the diagnosis.

Splenic Abscess and Infarct

- Splenic abscesses are associated with fever and tenderness in the left upper quadrant.
- Similar findings may be present in splenic infarction.
- Risk factors for splenic infarction such as atrial fibrillation, hypercoagulable state, sickle cell anemia, etc. may be present.
- Leukocytosis, high ESR in case of abscess.
- Ultrasound abdomen can confirm the presence of splenic abscess.

Q. Discuss the causes and differential diagnosis of acute lower abdominal pain.

Causes of Acute Lower Abdominal Pain

- Appendicitis
- Acute diverticulitis
- Ureteric colic
- Torsion of ovarian cyst
- Rupture of ectopic pregnancy

Appendicitis

- Common in young individuals.
- Pain is initially periumbilical. Later it shifts to right lower quadrant due to development of local peritonitis.
- Associated nausea and vomiting present.
- Tenderness and rebound tenderness positive in right iliac fossa.
- Ultrasound abdomen reveals swollen appendix or appendicular mass.

Acute Diverticulitis

- Usually occurs in older individuals.
- Pain is often present for several days prior to presentation.
- Pain occurs in the right or left lower quadrant.
- Abdominal tenderness.
- CT scan and contrast enema are helpful in diagnosis.

Ureteric Colic

- Past history of kidney stones may be present.
- Pain is severe and radiates from loin to groin. Pain comes on and off and paroxysms of severe pain last 20 to 60 minutes. Pain may radiate to the ipsilateral testicle, tip of the penis, or labia.
- Hematuria may be present.
- Nausea, vomiting, dysuria, and urgency may be present.
- Ultrasound abdomen and CT scan can confirm the diagnosis.

Ovarian Cyst

- Sudden onset lower abdominal pain often associated with waves of nausea and vomiting. However, this can occur in other conditions also and hence, nonspecific.
- Previous history of ovarian cyst/mass.
- History of recent vigorous activity.
- Ultrasound and CT-abdomen can confirm the diagnosis.

Rupture of Ectopic Pregnancy

- Women in reproductive age group.
- H/o amenorrhea present.
- Sudden onset lower abdominal pain with vaginal hemorrhage.
- Signs of hypovolemic shock may be present such as hypotension, tachycardia, and pallor.
- Pregnancy test positive. Hemoglobin low.
- Ultrasound abdomen confirms the diagnosis.

Q. Discuss the causes and differential diagnosis of diffuse abdominal pain.

Causes

- Mesenteric infarction
- Ruptured abdominal aortic aneurysm
- Diffuse peritonitis.
- Intestinal obstruction

Mesenteric Infarction

- Acute and severe onset of diffuse and persistent abdominal pain.
- Pain is out of proportion to physical findings.
- Patients have evidence of cardiovascular, ischemic, or atheriosclerotic disease.
- Stool occult blood may be positive.
- Angiography or MRI angiography of the celiac artery or mesenteric arteries can confirm the diagnosis.

Ruptured Aneurysm

- Patients present with abdominal or back pain
- Physical examination shows pallor, hypotension and a pulsatile abdominal mass.
- Ultrasound abdomen, CT or MRI can confirm the diagnosis.

Peritonitis

- Pain is diffuse and constant. It is aggravated by movement, coughing and deep breathing. Hence, patients with peritonitis lay down still, in supine position with the knees flexed.

- Patient appears sick.
- Fever, tachycardia and hypotension.
- Abdominal tenderness, rebound tenderness and guarding present.
- Bowel sounds are absent.
- Plain X-ray abdomen shows multiple air fluid levels and gas under diaphragm in case of visceral perforation causing peritonitis.

Intestinal Obstruction

- Pain is colicky and intermittent paroxysms of pain occur every four or five minutes.
- Associated vomiting, constipation and abdominal distension.
- Hypotension, oliguria, and dry mucous membranes indicate dehydration.
- Tenderness may be present.
- Tympanic note on percussion due to air filled bowel loops.
- Bowel sounds increase initially but later decrease.
- Plain X-ray abdomen shows multiple air fluid levels.
- Ultrasound abdomen, and CT abdomen can confirm the diagnosis and reveal the cause of obstruction.

Diseases of Nervous System

5

Q. Enumerate the common symptoms of nervous system disease.

- Headache and facial pain
- Weakness
- Movement disorders
- Speech and language disturbances
- Sensory disturbances
- Sphincter disturbances
- Memory disturbances
- Abnormal gait and posture
- Changes in personality and behavior
- Dizziness and blackouts
- Loss of balance
- Sleep disorders
- Acute confusional state (delirium)
- Coma and altered sensorium

Q. Enumerate the neuroimaging techniques.

- Nowadays many neuroimaging techniques are available which can help pinpoint the location and pathology of nervous system diseases. These include:
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)
  - Perfusion CT (pCT)
  - Perfusion MRI (pMRI)
  - CT angiography (CTA)
  - MR angiography (MRA)
  - Functional MRI (fMRI)
  - MR spectroscopy (MRS)
  - MR neurography
  - Positron emission tomography (PET)

Q. Computed tomography (CT) scan.

- CT is a cross-sectional image created by a computer using the data obtained by passing X-ray beams through a section of the body.
- An X-ray tube rotates axially around the patient, and a diametrically opposed array of detectors detect the radiation traversing the body. This data is converted to cross-sectional images with the help of powerful processors.
- Tissues such as bone which attenuate the X-ray more appear as high density areas while soft tissues with low attenuation appear as low density areas.
- A modern CT scanner is capable of obtaining sections as thin as 0.5 to 1 mm. Complete studies of the brain can be obtained in 20 to 60 seconds.
- CT is safe, fast, and reliable. Radiation exposure is between 3 and 5 cGy per study.
- In the helical CT the table with the patient moves continuously through the rotating X-ray beam, generating a "helix" of information that can be reformatted into various slice thicknesses.
- Multiple detectors can be positioned to detect the radiation which results in multiple slices per revolution of the X-ray beam around the patient. These "multidetector" scanners have greately reduced the time per examination of the patient.
- CT scan can be taken after giving intravenous contrast (contrast CT). This is helpful to identify vascular structures and to detect defects in the blood–brain barrier (BBB), which are associated with disorders such as tumors, infarcts, and infections. There are both ionic and non-ionic contrast agents. Ionic contrast agents can cause renal failure and allergic reactions which is not seen with non-ionic contrasts.

Indications for CT Scan

- Trauma to the head and spine
- Stroke
- Intracranial space occupying leisons
- Suspected subarachnoid hemorrhage
- Conductive hearing loss
- Evaluation of a suspected pathology in any part of the body.

Q. Magnetic resonance imaging (MRI).

- Magnetic resonance imaging is based on the magnetization properties of hydrogen protons in biologic tissues.
- The energy state of the hydrogen protons is transiently excited by an external powerful magnet. The subsequent return to equilibrium energy state (relaxation) of the protons results in a release of energy (the echo), which is detected and used to form a MR image.
- The MR image thus is a map of the distribution of hydrogen protons, with signal intensity depending on the density of hydrogen protons as well as differences in the relaxation time.
- MR images can be generated in sagittal, coronal, axial, or oblique planes without changing the patient's position. Three-dimensional imaging is also possible with MRI.
- The heavy-metal element gadolinium is used as intravenous MR contrast agent. Allergic reactions are rare with this agent and renal failure does not occur.
- MRI scanning can cause claustrophobia (fear of closed spaces) in some patients because the patient is moved into a long, narrow gap within the magnet. This can be reduced by mild sedation.
- Unlike CT, movement of the patient during an MR sequence distorts the images. Hence uncooperative patients should either be sedated for the MR study or go for CT scan.

Advantages of MRI over CT Scan

- No radiation exposure.
- Better delineation of soft tissue details.
- Clearly differentiates white and grey matter.
- Very useful in the evaluation of posterior fossa lesions where CT is not very accurate due to dense bony structures.
- Particulary useful to recognize demyelinating plaques as in multiple sclerosis.

Contraindications to MRI

The metallic parts of many medical devices and implants can get dislodged due to powerful magnetic field of the MRI. Hence, in the following situations, MRI is contraindicated.

- Cardiac pacemaker or permanent pacemaker leads.
- Internal defibrillatory device.
- Cochlear prostheses.
- Metallic bone implants.
- Electronic infusion devices.
- Intracranial aneurysm clips (metallic).
- Ocular implants (some) or ocular metallic foreign body.
- Swan-Ganz catheter.
- Magnetic dental implants.

Q. Magnetic resonance angiography (MRA).

- Moving protons (e.g. flowing blood, CSF) exhibit high to low signal intensity relative to background stationary tissue. This can be used to create angiography-like images, which can be manipulated in three-dimensions to highlight vascular anatomy.
- Through the selection of different imaging parameters, differing blood velocities can be highlighted and selective venous and arterial MRA images can be obtained.
- MRA can also be obtained during infusion of a contrast material called contrast-enhanced MRA which has become the standard for extracranial vascular MRA. Gadolinium-DTPA is used as contrast.
- MRA is not as good as conventional angiography for the detection of small-vessel detail, such as is required in the workup of vasculitis. MRA is also less sensitive in the presence of slowly flowing blood and thus may not differentiate complete from near-complete occlusions.
- However, despite of these limitations, MRA has become very important in evaluation of the extracranial carotid and vertebral circulation as well as of larger-caliber intracranial arteries and dural sinuses. It is also useful in the noninvasive detection of intracranial aneurysms and vascular malformations.

Q. Positron emission tomography (PET).

- Positron emission tomography (PET) allows the imaging of structures by virtue of their ability to concentrate molecules labeled with a positron-emitting isotope.
- PET scan is obtained by the detection of positrons emitted during the decay of a radionuclide that has been injected into a patient. The most frequently used moiety is fluorodeoxy-glucose (FDG), which is an analogue of glucose.
- Metabolically active cells, such as malignant cells, utilize and import more glucose than other tissues and thus take up FDG more avidly. Multiple images of glucose uptake activity are formed after 45 to 60 min. Images reveal differences in regional glucose activity among normal and pathologic brain structures.
- A lower activity of FDG in the parietal lobes is seen in Alzheimer's disease.
- Higher activity may be seen in malignant lesions and areas of seizure focus.

Q. Describe the technique, indications and contraindications of lumbar puncture.

Q. Composition of normal CSF.

- Lumbar puncture (LP) is the technique of obtaining CSF from the lumbar area for analysis. LP is useful in the diagnosis of a variety of infectious and noninfectious neurologic conditions.

Technique

- LP can be performed with the patient in the lateral recumbent position or sitting upright.
- The safe site of puncure is L3/4 or L4/5 interspace since this is well below the termination of the spinal cord. These spaces can be identified by drawing a line joining the highest points of the iliac crests. This line corresponds to L3/4 space.
- Correct patient positioning is important for the success of LP. The patient is instructed to remain in the fetal position with the neck, back, and limbs held in flexion. The overlying skin should be cleaned with alcohol and a disinfectant such as povidone-iodine. A sterile drape with an opening over the lumbar spine is then placed on the patient.
- Local anesthesia (lignocaine) is infiltrated into the lumbar intervertebral space and a 20 or 22 gauge spinal needle containing a stylet is inserted into the lumbar intervertebral space.
- The spinal needle should be advanced slowly in the direction of umbilicus. The bevel of the needle should face upwards to allow the needle to spread rather than cut the dural sac (the fibers of which run parallel to the spinal axis).
- As soon as the subarachnoid space is entered, there is loss of resistance to the insertion of needle. The stylet should be withdrawn to check for the CSF flow. If no CSF flow is detected the needle should be manipulated back and forth and rechecked for CSF flow.
- Once CSF begins to flow through the needle, the patient should be instructed to slowly straighten the legs to allow free flow of CSF within the subarachnoid space. A manometer should then be placed over the hub of the needle and the opening pressure should be measured. Fluid is then serially collected in sterile plastic tubes or bottles. A total of 8 to 15 ml of CSF is typically removed during routine LP.

Indications

- Diagnosis of meningitis.
- Suspected subarachnoid hemorrhage.
- CNS malignancies.
- Demyelinating conditions such as multiple sclerosis and Guillain-Barré syndrome (albuminocytologic dissociation is seen where there is increase in CSF albumin without increase in cells).
- For spinal anesthesia.
- Administration of intrathecal antibiotics and chemotherapeutic agents.
- As therapeutic in NPH (normal pressure hydrocephalus).
- Injection of contrast media for myelography or for cisternography.

Complications

- LP is a relatively safe procedure, but following complications can occur rarely.
- Post-LP headache.
- Infection (meningitis).
- Bleeding.
- Cerebral herniation.
- Radicular pain or numbness.
- Late onset of epidermoid tumors of the thecal sac.

Contraindications

- Bleeding diathesis (thrombocytopenia, coagulation defects).
- Infected skin over lumbar area.
- Raised intracranial pressure.

Composition of Normal CSF

Appearance	Clear, colourless
Pressure	60–150 mm of CSF
Proteins	20–40 mg/dl
Sugar	40–70 mg/dl
Chlorides	720–750 mg/dl
Cells (per mm^3)	0–5 (all lymphocytes)
Culture	Sterile

Q. Electroencephalography (EEG)

- EEG is the recording of electrical activity of the brain by electrodes placed on the scalp. The recorded activity represents the postsynaptic potentials of pyramidal cells of cerebral cortex.
- Normal EEG varies according to the patient's age and level of arousal.
- The electrical activity from any electrode pair can be described in terms of amplitude and frequency.
- The most important use of EEG is in the evaluation of epilepsy.

Normal EEG

- Amplitude ranges from 5 μV to 200 μV. Frequency of EEG activity ranges from 0 Hz to approximately 20 Hz. The frequencies are described by Greek letters: alpha, beta, theta and delta.

Alpha—8 to 13 Hz, seen in adults who are relaxed with their eyes closed. They disappear with eyes open. Alpha activity disappears normally with attention (e.g. mental arithmetic, stress, opening eyes).
Beta—More than 13 Hz, seen in people who are awake, with their eyes open or closed.
Theta—4 to 7 Hz, seen in sleep.
Delta—0 to 4 Hz, seen in deep sleep.

Abnormal EEG

- In routine EEG studies, some "activations" are used to bring out inapparent abnormalities. These activations include, hyperventilation for 3 mins, photic stimulation, and sleep deprivation on the night prior to the recording. These provocations are especially useful to activate epileptic activity.
- Increased generalized slow wave (theta and delta) activity is seen in metabolic encephalopathies.
- Focal slow wave activity is seen in focal brain lesions (e.g. tumor, infarct).
- Spike and sharp waves may be seen in epilepsy.
- Evoked potentials can be utilized to test the integrity of a pathway in the CNS. For example, in multiple sclerosis where there is demyelination of central neurons, conduction is slow and evoked potentials are delayed.

Q. Nerve conduction velocity studies (NCV studies).

- NCV studies are used to evaluate the integrity of peripheral nerves. Mainly sensory and motor nerves are tested.
- Conduction studies can assess the number of functioning axons by measuring the amplitude of action potential since each axon makes a contribution to the magnitude of the electrical field. The state of myelin sheath of axons can be assessed by the conduction velocity of action potential since the conduction velocity depends on intact myelin sheath.
- In patients with axonal degenerative neuropathies, such as diabetic neuropathy, the primary abnormality in NCV study is reduced sensory action potential amplitudes. Slowing of conduction is the primary feature in demyelinating neuropathies, such as Guillain-Barré syndrome, compression and entrapment neuropathies, such as carpal tunnel syndrome.

Q. Define weakness. How do you approach a case of weakness? How do you differentiate upper from lower motor neuron weakness?

- Weakness is reduction in normal power of one or more muscles.
- Paralysis and the suffix "-plegia" indicate weakness that is complete or nearly complete. "Paresis" refers to weakness that is mild or moderate.
- Weakness can be due to lesions anywhere in the motor cortex, corticospinal tracts, anterior horn cells, spinal nerve roots, peripheral nerves, neuromuscular junction, and muscles.

Table 5.1 Differences between upper and lower motor neuron weakness

Sign	Upper motor neuron leison	Lower motor neuron leison
Muscle atrophy	No	Yes
Fasciculations	No	Yes
Tone	Increased	Decreased
Distribution of weakness	Pyramidal/regional	Distal/segmental
Tendon reflexes	Exaggerated	Diminished
Babinski's sign	Extensor	Flexor
Superficial reflexes	Absent or decreased	Absent or decreased
Clonus	Present	Absent

Approach to a Case of Weakness

History

Is it really weakness or something else?

- Many patients with a variety of systemic disorders may misinterpret difficulties performing certain tasks as weakness. Examples are cardiopulmonary disease, joint disease, anemia, and cachexia from malignancy. Objective muscle power is normal in such cases.
- Patients with asthenia often complain of nospecific weakness. In comparison, patients with true weakness complain that they are unable to perform specific tasks, such as getting up from squatting position, climbing stairs or combing hair.

Distribution of weakness

- Distribution of weakness is also important. Diffuse (generalized) weakness occurs in myasthenia gravis, periodic paralysis, myopathies and advanced motor neuron disease.
- If the weakness is not generalized, it can be characterized as symmetric or asymmetric. Asymmetric weakness (e.g. hemiplegia) usually is due to central or peripheral nervous system disease.

- Symmetric weakness can be distal or proximal. Proximal weakness involves the axial muscle groups, deltoids, and hip flexors. Patients have difficulty in getting up from squatting position and to climb stairs. Patient also c/o difficulty in raising the upper limbs above the head. Proximal muscle weakness is seen in myopathies, muscular dystrophies, and myasthenia gravis.
- If weakness of a limb is associated with lower facial weakness on the same side, the problem is above the brainstem, while if there is weakness of muscles on one side of the head and opposite limb, then a lesion in the brainstem is suggested.
- Specific distributions of weakness are characteristic of certain neuropathies or muscular dystrophies. Examples are facioscapulohumeral dystrophy, scapuloperoneal dystrophy, and scapulohumeral dystrophy.

Associated symptoms/diseases

- H/o associated atrophy or fasciculations suggest damage to anterior horn cells or motor axons (i.e. lower motor neurons).
- Complaints of "numbness" or tingling suggest peripheral nerve involvement.
- A change in character of the voice or problems swallowing (usually choking on water) suggests involvement of pharyngeal muscles or those of the palate.
- Presence of bladder symptoms usually suggests spinal cord pathology.
- Presence of systemic diseases should be enquired because many systemic diseases can involve nervous system. For example, certain rheumatologic disorders can attack peripheral nerves. Several endocrine disorders, such as thyroid disorders can present with weakness. Diabetes mellitus causes peripheral neuropathy. Infections like tuberculosis, HIV, syphilis can affect nervous system. H/o malignancy should also be enquired.

Onset and course of weakness

- Sudden onset weakness suggests stroke (ischemic or hemorrhagic) or trauma.
- If repeated activity tends to worsen the weakness (for example, if there are things that patients cannot do at the end of the repeated activity that they could at the beginning), it suggests a diagnosis of myasthenia gravis.
- If weakness happens at random, with recovery after five to 30 minutes, transient ischemic atack should be considered.
- If the weakness is insidious onset, starting in lower limbs and gradually ascending upwards to involve upper limbs, in it suggests Guillain-Barré syndrome.
- If the weakness is insidious onset and very slowly progressive (over weeks to months), it suggests degenerative disorders (motor neuron disease) or malignancy.

Family history

- Family history is important in detecting hereditary neuropathies and myopathies. Some of the familial periodic paralysis problems may be hereditary.

Examination of Patient

- Examination is focused on confirming the pattern of weakness and determining the type of weakness.
- Exaggerated deep tendon reflexes, increased muscle tone (spasticity), and extensor plantar response suggest upper motor neuron (e.g. corticospinal tract) lesion in the brain or spinal cord.
- Absent or decreased deep tendon reflexes, decreased muscle tone, muscle atrophy, and muscle fasciculations suggest lower motor neuron lesion.
- If patients have hyporeflexia and predominantly distal muscle weakness, particularly with distal sensory deficits or paresthesias, suspect polyneuropathy.

Investigations

- Leisons can be vascular events (infarction/hemorrhage), inflammatory/immunologic, infectious, neoplastic, toxic, or metabolic in origin.
- Various investigations may help in identifying the exact nature of leison. These include CT and /or MRI imaging, NCV studies, etc.
- Elevation of muscle enzymes (creatine kinase) occurs in muscle diseases.
- Muscle biopsy may be necessary to determine the precise form of myopathy.

Q. Describe the pathway of upper motor neuron.

Q. Pyramidal tract.

- Upper motor neuron pathway consists of corticospinal and corticobulbar tracts.
- Upper motor neurons have their cell bodies in layer V of the primary motor cortex (the precentral gyrus, or Brodmann's area 4) and in the supplemental motor cortex (area 6).
- Axons of these neurons descend through the subcortical white matter and the posterior limb of the internal capsule.
- In the brainstem they pass through cerebral peduncle of the midbrain, the basis pontis, and the medullary pyramids.

- At the cervicomedullary junction, most pyramidal axons cross to opposite side and form lateral corticospinal tract. 10 to 30% remain ipsilateral in the anterior spinal cord to form anterior corticospinal tract.
- Finally the axons end on anterior horn cells of spinal cord through monosynaptic connections.
- Corticobulbar neurons are similar to corticospinal neurons but innervate brainstem motor nuclei.

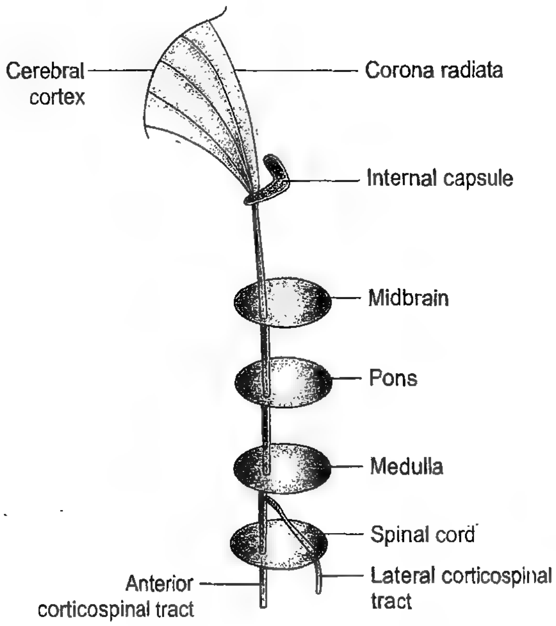

Fig. 5.1: Corticospinal tract

Q. Plantar reflex (Babinski sign).

- Plantar reflex is a nociceptive superficial reflex subserved by S1 segment.
- It was first described by Babinski.

Method of Elicitation

- Lateral part of sole is stroked with a blunt and narrow tip object (e.g. a key, or handle of a reflex hammer), starting near the heel and proceeding to the base of the little toe.

Normal Response

- Flexion of the big toe and adduction of other toes. This is called flexor plantar response.

Abnormal Response

- Extension of the big toe, with or without fanning out of other toes. It is called extensor plantar response or Babinski sign.

Causes of Extensor Plantar Response

- It is a sign of upper motor neuron lesion. It is found in lesions of corticospinal tract above S1. It is also found in metabolic encephalopathies and after an attack of epilepsy.
- Physiological: In infants, children below 2 years, and during deep sleep.

Equivocal Response

- This is neither flexor nor extensor and is difficult to interpret.

Q. Define coma. Describe the mechanism and causes of coma. How do you investigate and manage a case of coma?

- Coma is a clinical state in which patient is un-responsive to external stimulation and unarouseable ("unarouseable unresponsiveness").

Mechanisms of Coma

- Consciousness is maintained by an interaction of reticular activating system of brainstem and cerebral cortex. Hence, altered consciousness including coma can be produced by any pathology in the brainstem, reticular formation and cerebral cortex.

Table 5.2 Causes of coma

Diffuse brain dysfunction
- Drug overdose (sedatives, anesthetic agents, alcohol)
- CO poisoning
- Hypoglycemia
- Hyperglycemia (DKA, HHS)
- Hypoxic/ischemic brain injury
- Hypertensive encephalopathy
- Uremia
- Hepatic failure
- Respiratory failure
- Electrolyte imbalances (hypercalcemia, hypocalcemia, hyponatremia, hypernatremia)
- Endocrine causes (hypoadrenalism, hypopituitarism and hypothyroidism
- Metabolic acidosis
- Hypothermia, hyperpyrexia
- Trauma (following closed head injury)
- Epilepsy (following a generalized seizure)
- Infections (encephalitis, meningitis, cerebral malaria, sepsis)
- Subarachnoid hemorrhage
- Cerebral edema

Direct effect within brainstem
- Brainstem hemorrhage or infarction
- Brainstem neoplasm (e.g. glioma)
- Brainstem demyelination
- Wernicke-Korsakoff syndrome
- Trauma

Pressure effect on brainstem
- Hemisphere tumor, infarction, abscess, hematoma
- Cerebellar mass lesions

Examination of a Patient with Coma

Immediate Assessment

- Take care of CABs (Circulation, Airway, Breathings) first. If CABs are not alright take immediate measures to correct them.
- Get a quick short history from those who brought the patient. Many patients with diabetes, epilepsy or hypoadrenalism, carry identification which may give clue about the cause of coma.
- Record depth of coma by using Glasgow Coma Scale.
- Next go for full general and neurological examination.

General Examination

- Many general examination findings may provide clues to the cause of coma.
- *Temperature*: Body temperature is high in infection and hyperpyrexia, and low in hypothermia and hypothyroidism. Pontine hemorrhage also can cause elevated body temperature.
- *Cyanosis*: Coma may be due to respiratory failure or cardiac failure.
- *Jaundice*: Coma may be due to liver failure, sepsis.
- *Petechiae and purpura*: Coma may be due to intracranial bleed due to some bleeding problem.
- *Hyperpigmentation*: Coma may be due to Addison's disease.
- *Injection marks*: Coma may be due to drug abuse.
- *Coarse and dry skin*: Coma may be due to hypothyroidism.
- *Breathing*: Look for smell of ketones, alcohol, or ammonia. Arsenic poisoning produces the odor of garlic. OP compound poisoning produces kerosene smell. *Cheyne-Stokes (periodic) respiration* is alternating hyperapnea and apnea seen in bilateral cerebral dysfunction, or brainstem problem. It also occurs in metabolic comas and respiratory failure. *Kussmaul (acidotic) respiration* is deep, sighing hyperventilation seen in diabetic ketoacidosis and uremia.

Neurological Examination in Coma

- *Head, neck and spine*: Note trauma, skull burr-holes and bruits, neck stiffness.
- *Pupils*: Check size and reaction to light. Unilateral dilated pupil indicates compression of the third nerve due to temporal lobe uncus herniation (coning). This happens in raised intracranial pressure on one side (e.g. an extradural hematoma). Bilateral fixed, dilated pupils are seen in brainstem death, and deep coma of any cause. Bilateral pinpoint pupils are seen in pontine lesions (e.g. a pontine hemorrhage) and opioid intoxication.
- *Fundi*: Presence of papilloedema suggests raised intracranial tension. Look for retinal hemorrhage.
- *Ocular movements*: Vestibulo-ocular reflexes. Passive head turning produces conjugate ocular deviation away from the direction of rotation (doll's eye reflex). This reflex is absent in deep coma and brainstem lesions. In *caloric stimulation test*, ocular deviation towards the irrigated ear is seen when ice-cold water is irrigated into the external auditory meatus. This is also absent in brainstem death.
- *Abnormalities of conjugate gaze*: *Lateral deviation* occurs towards a destructive frontal lesion. Rarely, an irritative lesion in one frontal lobe can make the eyes deviate to opposite side. In a pontine lesion, conjugate lateral deviation occurs away from the lesion. *Skew deviation* (one eye deviated up and the other down) indicates a brainstem or cerebellar lesion.
- *Other findings*: Look for any asymmetry in tone, reflexes and plantar responses.

Cardiac Examination

- Cardiac diseases such as atrial fibrillation, infective endocarditis, MI, etc. can produce embolic stroke and cause coma.

Abdominal Examination

- Look for abnormal bowel sounds, organomegaly, masses, and ascites. Bowel sounds are absent in an acute abdominal condition, as well as with anticholinergic poisoning. Increased bowel sounds occur in organophosporus compound poisoning. Hepatomegaly is seen in hepatoma or metastatic disease which indirectly suggests brain metastases as the cause of coma. Look for evidence of cirrhosis such as ascites and splenomegaly which suggests hepatic encephalopathy as the cause of coma.

Respiratory System Examination

- Look for evidence of COPD, pneumonia or any other lung disease which can produce respiratory failure and coma.

Investigations

- Tests should be choosen according to the clues available from history and examination.
- Routine biochemistry (urea, creatinine, electrolytes, glucose, calcium, liver function tests)
- Metabolic and endocrine studies (TSH, serum cortisol)
- Blood cultures, malaria test to rule out cerebral malaria and sepsis.
- Drugs screen (e.g. diazepam, narcotics, etc.).

- Urine examination for ketone bodies
- Arterial blood gas analysis (hypoxia and hypercarbia can cause coma)
- *Imaging*: CT or MRI brain should be done to rule out any intracranial pathology.
- *CSFexamination*: This is helpful to rule out meningitis and subarachnoid hemorrhage.
- *Electroencephalography*: EEG is of some value in the diagnosis of metabolic coma, encephalitis and ongoing non-convulsive seizures.

Management

Specific Treatment

- The underlying cause of coma should be treated. For example, correction of blood glucose in hypoglycemia.

General Measures

- Ryle's tube and a urinary catheter should be passed.
- Skin care—frequent turning of patient to avoid pressure sores. Patient should be kept preferably in water bed to prevent pressure sores.
- Oral hygiene—mouth washes, frequent suction.
- Eye care—taping of lids, prevention of corneal damage by applying lubricating eye drops and eye ointment.
- Nutrition and hydration—food and water may be given through Ryle's tube. IV fluids may also be used if required.

Q. Glasgow Coma Scale (GCS)

- The Glasgow Coma Scale (GCS) is a way to grade coma severity. It was introduced to assess the conscious level of patients with acute brain injury from head trauma, intracranial hemorrhage and many other causes. The GCS reflects the initial severity of brain dysfunction, while serial assessments demonstrate the evolution of the injury.

  Three parameters are used for this purpose; eye response (E), verbal response (V), and motor response (M). It is easy to use and has good interobserver reliability.
- The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. A score of 13 or higher correlates with mild brain injury; a score of 9 to 12 correlates with moderate injury; and a score of 8 or less represent severe brain injury.
- The GCS is useful for prognosis, but does not aid in the diagnosis of coma.

Eye opening	
Spontaneous	4
To sound	3
To pain/pressure	2
No eye opening	1
Verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Motor response	
Obeys commands	6
Localizing response to pain	5
Withdrawal response to pain	4
Flexion to pain	3
Extension to pain	2
No motor response	1

[Remember EVM; 4, 5, 6]

Q. Locked-in syndrome.

- This occurs when a lesion damages the bilateral ventral pons. Examples of such lesions are pontine hemorrhage, pontine abscess, brainstem tumors, and central pontine myelinolysis. Locked-in syndrome most often is observed as a consequence of pontine infarction due to basilar artery thrombosis.
- Patients are alert and aware of their environment but are quadriplegic, with lower cranial nerve palsies resulting from bilateral ventral pontine lesions that involve the corticospinal, corticopontine, and corticobulbar tracts. Only vertical eye movement and opening and closing of eyes are possible.
- EEG is normal as the brain is normal. Majority of people die but some may live for many years.

Q. Brain death.

- Brain death implies permanent absence of cerebral and brainstem functions.

Establishing the Diagnosis

- In order to establish brain death, the irreversibly comatose patient must be shown to have lost all brainstem reflex responses, including the pupillary, corneal, oculo-vestibular, oculocephalic, oropharyngeal, and respiratory reflexes, and should have been in this condition for at least 6 hours.
- Spinal reflex movements may be present even in brain death and do not exclude the diagnosis.

- Ongoing seizure activity or decerebrate or decorticate posturing is not consistent with brain death.
- The apnea test (presence or absence of spontaneous respiratory activity at a $PaCO_2$ of at least 60 mm Hg) serves to determine whether the patient is capable of respiratory activity.
- Some conditions may mimick brain death and these should be excluded. Such conditions are: Hypothermia (temperature <32°C) and overdosage with central nervous system depressant drugs.
- An isoelectric EEG is helpful in confirming the diagnosis but not necessary.

Prognosis

- Patients with brain death are unlikely to survive for more than a week.

Q. Persistent vegetative state (coma vigil).

- It occurs due to extensive cortical gray or subcortical white matter lesions with relative preservation of brain stem.
- This state follows coma and is characterized by absence of cognitive function or awareness of the environment despite a preserved sleep/wake cycle. Spontaneous movements may occur, and the eyes may open in response to external stimuli, but the patient does not speak or obey commands.
- There is no purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli.
- No evidence of language comprehension or expression.
- Hypothalamic and brainstem autonomic functions are intact so that there is spontaneous respiration and other brainstem reflexes.
- There will be bowel and bladder incontinence.

Q. Ptosis.

- Ptosis refers to drooping of the upper eyelid.
- Ptosis is the result of dysfunctioning of one or both upper eyelid elevator muscles. These elevator muscles are the levator palpebrae superioris and the Müller's muscle. The levator palpebrae superioris is a striated muscle innervated by the oculomotor nerve. The Müller's muscle is a smooth muscle, innervated by sympathetic system.
- Ptosis can be disabling, if it obstructs vision.

Treatment

- Treat the underlying cause.
- Patients with obstructed vision can be considered for surgical correction.

Table 5.3 Causes of ptosis

Causes	Features
• Congenital ptosis	Usually unilateral. Many patients also have amblyopia, strabismus
• 3rd nerve palsy	Usually unilateral. Pupil is dilated on the affected side
• Horner's syndrome	Usually unilateral. Pupil is constricted on the affected side
• Myasthenia gravis	Usually bilateral. Pupils are normal size. Degree of ptosis variable. Associated diplopia often present
• Muscle disease	Usually bilateral. Pupils are normal size
• Mechanical ptosis	Usually unilateral. Occurs due to excess weight on the upper lid. Examples are eyelid tumors.

Q. Papilledema.

- Papilledema refers to swelling of optic disc.
- In papilledema, there is axonal swelling within the optic nerve, blockage of axonal transport with capillary and venous congestion.
- Pseudopapilledema—congenital anomalies of the disc, including drusen and myelinated nerve fibers, may cause the appearance of disc swelling or pseudopapilledema.

Causes of Papilledema

Raised intracranial pressure
- Space occupying lesions (brain tumour, abscess, hematoma)
- Subarrachnoid hemorrhage
- Idiopathic intracranial hypertension
- Meningitis, encephalitis

Optic nerve disease
- Optic neuritis (e.g. multiple sclerosis)
- Optic neuropathy (hereditary, ischemic and toxic)

Venous occlusion
- Cavernous sinus thrombosis
- Central retinal vein thrombosis/occlusion
- Orbital mass lesions

Other causes
- Hypercapnia
- Optic nerve glioma
- Malignant hypertension
- Vasculitis (e.g. SLE)

Clinical Features

- Early papilledema is usually asymptomatic. However, as it progresses, enlargement of the blind spot and blurring of vision develop. In severe papilledema, arterial blood flow falls and infarction of the optic nerve occurs leading to severe and permanent visual loss.

- Diffuse headache and vomiting may be present if the cause of papilledema is due to raised intracranial pressure. The earliest ophthalmoscopic signs of disc swelling are pinkness of the disc followed by blurring of the nasal margin. Later there is loss of normal venous pulsation, and obliteration of physiological cup. Small hemorrhages may be present around the disc.

Investigations

- Neuroimaging (e.g. CT scan, MRI) of the brain should be done to rule out any mass lesion.
- Magnetic resonance (MR) venography to detect venous sinus thrombosis.
- Lumbar puncture (after ruling out mass lesion) and CSF analysis to identify any infectious or neoplastic disease.
- If there is doubt about disc edema, fluorescein angiography can be used to confirm it. Fluorescein is injected intravenously and if there is edema, it leaks in the retina.

Treatment

- Treat the underlying cause.
- *Diuretics*: The carbonic anhydrase inhibitor, acetazolamide (Diamox), is useful in selected cases, especially idiopathic intracranial hypertension.
- Lumboperitoneal shunt or ventriculoperitoneal shunt can be used to bypass CSF.

Q. Optic neuritis.

Q. Retrobulbar neuritis.

- Optic neuritis is inflammation of the optic nerve.
- Retrobulbar neuritis refers to optic nerve inflammation behind the eyeball. There is no abnormality seen at the disc but there is severe visual impairment.

Causes

- *Demyelinating diseases*: The most common cause of optic neuritis is demyelination (e.g. multiple sclerosis).
- *Infections*: Measles, mumps, influenza, varicella-zoster virus, sinusitis, meningitis, TB, syphilis, HIV, etc.
- *Autoimmune disorders*: Particularly systemic lupus erythematosus.
- *Chemicals and drugs*: Lead, methanol, quinine, arsenic, antibiotics.

Clinical Features

- A history of preceding viral illness may be present. Patients are usually young adults and present with impairment of vision in 1 eye or, less commonly, both eyes.
- Dyschromatopsia (change in color perception may be present.
- Presence of retro-orbital or ocular pain, usually exacerbated by eye movement.
- Pupillary light reaction is decreased in the affected eye and various types of visual field defects are present.

Investigations

- MRI is very useful in assessing inflammatory changes in the optic nerves and to rule out structural lesions.
- Visual evoked potentials are abnormal in optic neuritis. They may be abnormal even when MRI of the optic nerve is normal.

Treatment

- IV steroids (methylprednisolone 250 mg qid for 3 days followed by rapid taper speed the rate of recovery.
- Plasma exchange has been used in patients with no significant improvement with steroids.

Q. Optic atrophy.

- *Optic atrophy* refers to the death of the retinal ganglion cell axons that comprise the optic nerve. It is the final common endpoint of any disease process that causes axon degeneration in the retinogeniculate pathway.
- *Primary optic atrophy*: Here the optic nerve fibers degenerate in an orderly manner and are replaced by glial cells without alteration of optic nerve head. It happens due to direct optic nerve damage from many causes.
- *Secondary optic atrophy*: Refers to optic atrophy secondary to papilledema due to any cause.

Causes of Optic Atrophy

- *Primary optic atrophy*: Infarction of the nerve from thromboembolism, inflammation (multiple sclerosis, syphilis), optic nerve compression, trauma, toxic (quinine and methyl alcohol), vitamin B_{12} deficiency.
- *Secondary optic atrophy*: Raised intracranial pressure due to various reasons, cavernous sinus thrombosis.

Clinical Features

- The main symptom is vision loss.
- Fundoscopy shows characteristic pale optic disc.

Treatment

- Treat the underlying cause.

Q. Describe the visual pathway. Describe briefly the field defects produced at various levels with appropriate diagrams.

Visual Pathway

- Whenever we see an object, its image falls on the retina. The image is converted to nerve action potentials by retinal rod, cone and ganglion cells.
- The axons of ganglion cells of retina form optic nerve. From each eye, one optic nerve starts. Both optic nerves cross in the optic chiasma.
- At the chiasma fibers from the nasal portion of retina cross, whereas fibers from temporal side of retina do not cross.
- Crossed nasal fibers join uncrossed temporal fibers and form optic tract. Optic tract reaches lateral geniculate body and synapses there. Some optic tract fibers reaching the lateral geniculate bodies pass to the brainstem to control refraction (lens) and pupillary aperture.
- From the lateral geniculate body, fibers pass in the optic radiation to reach the occipital cortex.
- In the optic radiation fibers from upper part of retina (representing lower visual field) lie above (parietal lobes) and those from lower part of retina (representing upper visual field) lie below in the temporal lobes.

Table 5.4 Visual field defects due to lesions at various lavels of optic pathway

Level of leison	Field defect
1. Optic nerve	Complete blindness on the side of leison
2. Lateral side of optic chiasma	Left scotoma and right upper quadrantanopia
3. Midline optic chiasma	Bitemporal hemianopia
4. Optic tract	Homonymous hemianopia (opposite side)
5. Lower optic radiation	Upper quadrantanopia (opposite side)
6. Upper optic radiation	Lower quadrantanopia (opposite side)
7. Complete optic radiation	Homonymous hemianopia with macular sparing

Q. Causes of pipoint pupils.

- Pontine hemorrhage
- Opiate poisoning
- Organophosphate poisoning
- Drugs (pilocarpine drops, timolol drops)

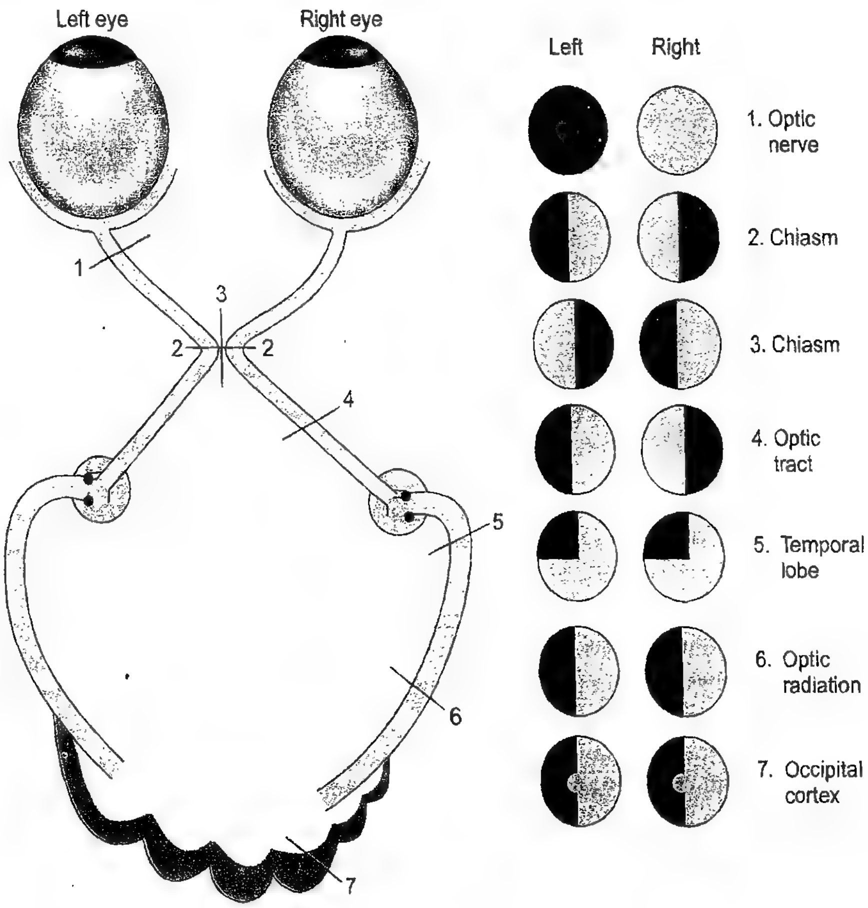

Fig. 5.2: Optic pathway and visual field defects

Q. Argyll Robertson pupil (ARP).

- ARP refers to pupils which constrict on a near object (they "accommodate"), but do *not* constrict when exposed to bright light (remember the pnemonic ARP—accommodation reflex present).
- The location of the lesion is believed to be in the dorsal midbrain lesion that interrupts the pupillary light reflex pathway but spares the more ventral pupillary near reflex pathway. A partial lesion in the third nerve or the ciliary ganglion has also been considered as a cause.
- *Causes*:
  - Tabes dorsalis (due to syphilis)
  - Pinealomas
  - Multiple sclerosis
  - Diabetes mellitus
- Argyll Robertson pupil should not be confused with Adie's pupil, which may yield a similar result. Adie's pupil is caused by ciliary ganglion destruction, and the reaction to light is absent or greatly diminished. However, Adie's pupil does react slowly with prolonged maximal stimulation. Furthermore, once the Adie's pupil reacts to accommodation, the pupil tends to remain tonically constricted and dilates very slowly.

Q. Horner's syndrome.

- Horner syndrome (Horner's syndrome) results from an interruption of the sympathetic nerve supply to the eye and is characterized by the classic triad of miosis (i.e. constricted pupil), ptosis, and anhidrosis.
- This sympathetic pathway originates in the hypothalamus, runs through the brainstem and spinal cord, sympathetic trunk, brachial plexus, and carotid plexus.

Causes

- Central (e.g. brainstem ischemia, syringomyelia, brain tumor).
- Peripheral (e.g. pancoast tumor, cervical adenopathy, neck and skull injuries, aortic or carotid dissection, thoracic aortic aneurysm).

Clinical Features

- Classic signs of a Horner's syndrome are ptosis, miosis, and anhidrosis on the affected side.
- Ptosis is due to paralysis of the Müller's muscle, supplied by sympathetic pathway. Miosis is due to loss of sympathetic dilator action on pupil. Anhidrosis happens because sweat glands are supplied by sympathetic system.
- Loss of ciliospinal reflex on the affected side.
- Enophthalmos.

Diagnosis

- *Confirmation of Horner's syndrome*: Cocaine drops cause pupilary dilatation in normal eyes whereas it has no effect in eyes with impaired sympathetic innervation. Cocaine acts by blocking the reuptake of norepinephrine at the sympathetic nerve synapse and causes pupillary dilation in patients with intact sympathetic supply.
- Imaging studies (CT or MRI) may be required to locate the site and nature of lesion.

Treatment

- Depends on the underlying cause.

Q. Diplopia.

- Diplopia is seeing two objects when there is actually one object. Diplopia is due to problems in the extraocular muscles or nerves supplying them.
- Diplopia may be monocular or binocular. Monocular diplopia is present when only one eye is open. Binocular diplopia disappears when either eye is closed.

Causes of Diplopia

- *Monocular diplopia*: Corneal distortion or scarring, multiple openings in the iris, cataract or subluxation of the lens, vitreous abnormalities.
- *Binocular diplopia*: Cranial nerve (3rd, 4th, or 6th) palsy, myasthenia gravis, orbital infiltration (e.g. thyroid infiltrative ophthalmopathy, orbital pseudotumor).

Evaluation of a Case of Diplopia

History and Examination

- Ask whether diplopia is monocular or binocular. Does covering either eye make the diplopia disappear? This test helps to rule out monocular diplopia, which persists in one eye even if the other eye is covered.
- Ask whether the images are separated vertically, horizontally, or both. Horizontal diplopia suggests 6th nerve palsy. Vertical diplopia suggests 4th nerve palsy. Intermittent diplopia suggests a waxing and waning neurologic disorder, such as myasthenia gravis.
- Take a detailed neurologic history.
- Look for the presence of any squint and check the eyeball movements in all directions. If an eyeball is unable to move in a particular direction it suggests 3rd, 4th or 6th nerve palsy as the cause of diplopia.
- Look for presence of ptosis. Ptosis occurs in 3rd nerve palsy and myasthenia gravis.

Investigations

- CT or MRI of the brain and orbit to rule out any intracranial or orbital pathology.
- Tensilon test if myasthenia gravis is suspected.

Treatment

- Patching one eye prevents double vision and allows the patient to continue functioning while awaiting resolution or intervention.
- Stick-on occlusive lenses can be applied to glasses to minimize the cosmetic handicap of a patched eye, while blurring one eye to minimize double vision.
- Strabismus surgery is occasionally necessary. Recession/ resection of extraocular muscle, transposition of extraocular muscle, weakening or shortening surgery are helpul in reducing double vision.
- *Chemodenervation*: Injection of botulinum toxin into the medial rectus muscle to reduce contracture due to a weak lateral rectus muscle.

Q. Apraxia.

- Apraxia is inability to perform a learned motor act in the absence of pyramidal, extrapyramidal, cerebellar, or sensory dysfunction. Apraxia occurs in frontal and parietal lobe lesions.
- Apraxia can be elicited by asking the person to perform a motor act which he new earlier, for example, lighting a cigarette, brushing teeth, etc.

Types

- *Ideomotor apraxia*: Here the person is unable to carry out a motor command, e.g. lighting a cigarette and brushing teeth. It is seen in left parietal lobe lesions.
- *Dressing apraxia*: Here the person is unable to wear his dress. It is seen in right parietal lobe lesions.
- *Constructional apraxia*: Here the person is unable to copy simple diagrams or build simple blocks. It is seen in right parietal lobe lesions.
- *Ideational apraxia*: Here the affected body parts appear to suffer from the absence of a basic plan, although many spontaneous actions are easily carried out. Patients appear uncertain about what to do next. It occurs in lesions of the posterior half of the dominant hemisphere.

Treatment

- Treatment includes speech therapy, occupational therapy, and physical therapy.
- Underlying cause has to be treated.

Q. Aphasia.

Q. Sensory aphasia.

Q. Motor aphasia.

Aphasia

- Aphasia is defined as an acquired disorder of language caused by brain damage. It must be distinguished from congenital or developmental language disorders like dyslexias.
- It results from dysfunction of the language centers in the cerebral cortex and basal ganglia or of the white matter pathways that connect them. In right-handed people and about two-thirds of left-handed people, language function resides in the left hemisphere.
- Aphasia can be broadly classified as sensory aphasia and motor aphasia.

Sensory Aphasia (Wernicke's Aphasia)

- Here the person is not able to comprehend verbal or written language. But able to speak fluently though not meaningfully. Hence, also called "empty speech". Patient chooses inappropriate words during speech (paraphasia).
- Reading is also affected.
- Sensory aphasia is produced by damage to posterior part of the superior temporal gyrus in dominant hemisphere (Wernicke's area or area 22). Damage may be due to infarction, hemorrhage, tumors, trauma and infections.

Motor Aphasia (Broca's Aphasia)

- Here the ccomprehension of spoken speech is relatively preserved but the speech is non-fluent. Speech consisists of few, poorly articulated words described as telegraphic speech. But the speech is meaningful and allows the patient to communicate with others in spite of deficient word output.
- Naming and writing are also affected.
- Motor aphasia is caused by damage to dominant posterior inferior frontal lobe (Broca's area or area 44). Damage may be due to infarction, trauma, tumors, infection and abscess.

Diagnosis

- Exclude other communication problems such as severe dysarthria, impaired hearing, impaired vision (e.g. when assessing reading), or motor writing ability.
- *Detailed neurological examination*: Bedside speech assessment includes the following:
  - *Spontaneous speech*: Speech is assessed for fluency (ease and rapidity of producing words), number of

words spoken, ability to initiate speech, presence of spontaneous paraphasic errors (e.g. "fork" for "spoon"), word-finding pauses, hesitations, and prosody (the emotional intonation of speech).
  - *Naming*: The patient is asked to name simple objects such as a key, pencil, coin, watch, parts of the body (nose, ear, chin, fingernail, knuckle), or to name colors.
  - *Repetition*: Patients are asked to repeat grammatically complex phrases (e.g. "no ifs, ands, or buts"). Patients with impaired repetition may omit words, change the word order, or commit paraphasic errors.
  - *Comprehension*: Patients are asked to point to objects named by the clinician, carry out one-step and multistep commands, and answer simple and complex yes-or-no questions.
  - *Reading and writing*: Patients are asked to write spontaneously or to dictation and to read aloud. Reading comprehension, spelling, and writing in response to dictation are assessed.
  - Brain imaging (CT or MRI) to identify the brain pathology.

Treatment

- Treatment of cause
- Speech therapy
- Augmentative communication devices (e.g. a book or communication board that contains pictures or symbols of a patient's daily needs, computer-based devices).

Q. Enumerate the causes of headache.

- Headache is a very common complaint reported by patients. Most people experience headache at least once during life.
- Most causes of headache are benign, but rarely headache can be due to potentially life-threatening central nervous system (CNS) diseases such as brain tumor, intracranial hemorrhage, etc.

Causes of Headache

Primary Headache Disorders

- Migraine
- Tension headache
- Cluster headache

Secondary Headache Disorders

- Subarachnoid hemorrhage
- Intracranial space occupying lesion (brain abscess, tumor, hematoma, AV malformation)
- Cortical vein thrombosis
- Severe hypertension
- Meningitis
- Temporal arteritis
- Metabolic disturbances (hypoxia, hypercarbia, hypoglycemia)
- Glaucoma
- Sinusitis
- Idiopathic intracranial hypertension (pseudotumour cerebri).

Q. Describe the classification, pathophysiology, clinical features and treatment of migraine headache.

- Migraine is recurrent headache associated with visual and gastrointestinal disturbance. Though migraine is a benign headache, attacks of headache are usually severe.
- Migraine can be classified into three types:
  - Migraine with aura (old term: classic migraine)
  - Migraine without aura (old term: common migraine)
  - Migraine variants (retinal migraine, ophthalmoplegic migraine, familial hemiplegic migraine, basilar migraine).

Epidemiology

- The prevalence of migraine is high. It is three times more common in women than men. It tends to run in families, and more common in young females. Migraine without aura (classic migraine) is the most common type (80 percent of all migraine cases).

Pathophysiology

- The exact cause of migraine is unknown. However, various theories have been put forward and various brain abnormalities have been found in patients with migraine.
- Migraine has a strong genetic component. Approximately 70% of migraine patients have a first-degree relative with a history of migraine. The risk of migraine is increased 4-fold in relatives of people who have migraine with aura.
- Migraine was previously thought to be a vascular phenomenon that resulted from intracranial vasoconstriction followed by rebound vasodilation. Currently, however, the neurovascular theory considers migraine as primarily a neurogenic process with secondary changes in cerebral perfusion associated with a sterile neurogenic inflammation.
- Migraineurs have been found to have neuronal hyperexcitability in the cerebral cortex, especially in the occipital cortex. A phenomenon called cortical spreading depression (CSD) (well-defined wave of neuronal excitation in the cortical gray matter that spreads from its site of origin) has been found in patients with aura. This cellular depolarization causes aura phase, which in

5

turn, activates trigeminal fibers, causing the headache phase. Activation of the trigeminovascular system by CSD stimulates nociceptive neurons on dural blood vessels to release plasma proteins and pain-generating substances such as calcitonin gene-related peptide, substance P, vasoactive intestinal peptide, and neurokinin A. The resultant state of sterile inflammation is accompanied by further vasodilation, producing pain. The serotonin receptor (5-hydroxytryptamine [5-HT]) is believed to be the most important receptor in the headache pathway and is found in trigeminal sensory neurons.

Migraine Precipitants

Various precipitants of migraine have been identified, which are as follows:

- Hormonal changes, such as those accompanying menstruation (common), pregnancy, and ovulation
- Stress
- Excessive or insufficient sleep
- Excessive exercise
- Eyestrain or other visual triggers
- Medications (e.g. vasodilators, oral contraceptives)
- Exposure to bright or fluorescent lighting
- Loud noises
- Strong odors (e.g. perfumes, colognes, petroleum distillates)
- Weather changes
- Motion sickness
- Certain food items (ice cream, chocolate, cheese)
- Hunger
- Red wine

Clinical Features

- Three phases of migraine can be recognized:
  - Premonitory symptoms
  - Aura
  - Headache
- ***Premonitory symptoms***: Precede an attack of migraine. These include fatigue, concentration difficulty, sensitivity to light or sound, nausea, blurred vision, yawning, etc.
- ***Aura***: Migraine aura is a transient neurologic symptom due to transient focal neurological dysfunction. Auras typically occur before the onset of migraine headache, and the headache usually begins simultaneously with or just after the end of the aura phase. Most auras last for less than one hour. Auras can be visual disturbances (blurring of vision, fortification spectra, light flashes), sensory symptoms, motor weakness and speech disturbances.
- ***Headache***: See the HIS criteria.

IHS (international headache society) criteria to diagnose migraine

Table 5.5 IHS diagnostic criteria for migraine without aura

A. At least 5 attacks fulfilling criteria B to D

B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia

E. Not attributed to another disorder

Table 5.6 IHS diagnostic criteria for migraine with aura

At least 2 attacks of migraine with following features: Aura consisting of at least one of the following, but no motor weakness:
1. fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)
2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
3. fully reversible dysphasic speech disturbance

At least two of the following:
1. homonymous visual symptoms[1] and/or unilateral sensory symptoms
2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
3. each symptom lasts ≥5 and ≥60 minutes

Investigations

- Migraine is a clinical diagnosis. Hence, investigations are ordered only if an organic pathology is suspected or to rule out any comorbid illness.
- ***Complete blood count:*** To rule out anemia. High ESR is seen in giant cell arteritis (temporal arteritis) which can mimick migraine.
- ***Neuroimaging (CT or MRI of head):*** This is not routinely necessary. It is indicated in following situations: first or worst severe headache, change in the pattern of previous migraine, abnormal neurologic examination, onset of migraine after age 50 years, in immunocompromised patient, headache with fever, and migraine with epilepsy.

- **Lumbar puncture** is indicated in following situations: First or worst headache of a patient's life, progressive headache, unresponsive, chronic, intractable headache.
- **Calcitonin gene-related peptide** (CGRP): Serum level of CGRP is elevated in most migraine patients. It is a neurotransmitter that causes vasodilation and can aid in the diagnosis of chronic migraine by serving as a biomarker for permanent trigeminovascular activation.

Management

Treatment of an Acute Attack

- Paracetamol or any other simple analgesics should be given, with an antiemetic such as metoclopramide if necessary. Analgesics are more effective if started in the beginning of headache.
- Triptans (5-HT, agonists) can also abort an attack. These include sumatriptan, zolmitriptan, naratriptan and rizatriptan.
- During an attack rest in a dark and quiet room.

Prophylaxis

- Avoid precipitating factors.
- The following drugs are used to prevent migraine attacks if they are very frequent:
- Beta blockers such as atenolol, metoprolol, and propranolol. Propranolol 10 mg three times daily, increasing to 40–80 mg three times daily.
- *Antidepressants*: Amitriptyline, clomipramine, mirtazapine.
- *Calcium-channel blockers*: Verapamil, nifedipine.
- *Antiepileptics*: Sodium valproate, topiramate.

Q. Cluster headache.

- Cluster headache (CH) is characterized by repetitive headaches that occur for weeks to months at a time (i.e. occurring in clusters), followed by periods of remission.

Etiology

- The exact cause of CH is unknown. The disorder is sporadic but rarely can be inherited.
- Several factors can provoke CH attacks. Subcutaneous injection of histamine provokes attacks in many patients. Stress, allergens, seasonal changes, or nitroglycerin and alcohol may trigger attacks. Many patients with CH are heavy smokers and alcoholics.

Pathophysiology

- The exact pathophysiology of CH is incompletely understood. Substance P neurons, vascular dilatation, functional hypothalamic dysfunction, central disinhibition of the nociceptive and autonomic pathways have been implicated in the causation of headache and autonomic disturbances.

Clinical Features

- It is a rare cause of headache and usually affects males between 30 and 40.
- Headache is strictly unilateral, usually deep, excruciating, felt around one eye and may last for several hours.
- CH is associated with ipsilateral autonomic symptoms such as lacrimation and redness of the eye, stuffy nose, rhinorrhea, sweating, pallor, and Horner's syndrome.
- Nausea and vomiting can also occur.
- Vasodilatation may be responsible for the pain and autonomic features of cluster headaches.
- Activation of hypothalamus has been noted during the attack of headache.

Treatment

Acute Attack

- Oxygen inhalation (9 L/min via a face mask) is the most effective therapy.
- Triptans (e.g. sumatriptan, 6 mg subcutaneously) can also be used to abort an attack.
- Dihydroergotamine can be an effective abortive agent.

Prevention of Attacks

- The best treatment is to prevent cluster attacks until the bout is over by using prophylactic medications.
- Prophylactic drugs are prednisolone, lithium, methysergide, ergotamine, sodium valproate, and verapamil.
- A 10-day course of prednisone, beginning at 60 mg daily for 7 days followed by a rapid taper, may prevent headache.
- Ergotamine can also prevent the attacks if given 1 to 2 h before an expected attack.
- Various invasive nerve blocks and ablative neurosurgical procedures (e.g. percutaneous radiofrequency ablation, trigeminal gangliorhizolysis, and rhizotomy) can be considered in refractory CH.

Q. Idiopathic intracranial hypertension (pseudotumor cerebri).

- Idiopathic intracranial hypertension (IIH) (pseudotumor cerebri) is a disorder of unknown etiology characterized by elevated intracranial pressure (ICP), headache and papilledema.

Etiology

- There is no hydrocephalus or an identifiable cause for increased CSF pressure. Raised intracranial pressure probably results from impaired CSF absorption by the arachnoid villi. The following are risk factors for developing idiopathic intracranial hypertension.
- Most cases occur in young women who are obese. Patients with higher body mass indexes (BMIs) and recent weight gain are at increased risk.
- *Drugs*: Amiodarone, antibiotics (e.g. nalidixic acid, penicillin, and tetracycline), carbidopa, levodopa, (topical and systemic), cyclosporine, oral contraceptives, phenytoin, and vitamin A (>100,000 U/day).
- *Systemic diseases*: Hypothyroidism, Cushing's disease, anemia, chronic respiratory failure, hypertension, multiple sclerosis, chronic kidney disease, Reye syndrome, sarcoidosis, etc.

Clinical Features

- Patients with IIH usually present with symptoms related to increased intracranial pressure (ICP) and papilledema.
- *Symptoms of increased intracranial pressure (ICP)*: diffuse headache worsened by coughing and straining, and worse in the morning. Diplopia can occur due to increased intracranial pressure causing abduscent nerve palsy.
- *Symptoms due to papilledema*: Transient visual disturbances, enlarged blind spots and loss of peripheral visual fields. Optic atrophy can lead to permanent loss of vision.

Diagnosis

- The diagnosis is made by lumbar puncture (CSF pressure higher than 250 mm Hg; normal CSF composition) after excluding a mass lesion by neuroimaging.

Treatment

- Intracranial pressure should be reduced to prevent visual loss.
- Weight reduction can help to some extent.
- Drugs to reduce intracranial pressure include acetazolamide and furosemide.
- Repeated lumbar punctures may be useful if drug treatment is ineffective.
- If all these measures fail, surgical options include optic nerve fenestration and ventricular-peritoneal shunting of CSF.
- Spontaneous recovery may sometimes occur.

Q. Enumerate the causes of facial pain.

Q. Discuss the etiology, clinical features and management of trigeminal neuralgia.

Causes of Facial Pain

- Trigeminal neuralgia
- Postherpetic neuralgia
- Glossopharyngeal neuralgia
- Occipital neuralgia
- Superior laryngeal neuralgia
- Carotodynia
- Carotid artery dissection
- Post-traumatic facial pain
- Sinusitis
- Dental pain
- Persistent idiopathic (atypical) facial pain
- Thalamic pain
- Cancer

Trigeminal Neuralgia (Tic Douloureux)

- Trigeminal neuralgia (TN) is sudden, usually unilateral, severe, brief, stabbing or lancinating, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve.

Epidemiology

- The annual incidence of TN is 4 to 5 per lakh population.
- It is one of the most common causes of facial pain in the elderly. Most cases begin after age 50.
- It is slightly more common in women.

Etiopathogenesis

- Most cases of trigeminal neuralgia are caused by compression of the trigeminal nerve root.
- Compression by an aberrant loop of an artery or vein accounts for 80 to 90 percent of cases. Other causes of nerve compression include acoustic neuroma, meningioma, epidermoid cyst, saccular aneurysm or arteriovenous malformation.
- Compression leads to demyelination of the nerve in the area around the compression. Demyelination results in ectopic impulse generation and crossing of impulses between fibres. Touch sensation impulses may cross into fibers carrying pain sensation and lead to pain.
- Demyelination may also be caused by multiple sclerosis and lead to trigeminal neuralgia.

Clinical Features

- The pain of trigeminal neuralgia occurs in paroxysms and is maximal at the onset.

- The pain is described as "electric shock-like" or "stabbing" and is unilateral in most cases.
- It usually lasts from one to several seconds, and does not awaken the patient at night. Episodes may last weeks or months.
- Facial muscle spasms can be seen with severe pain. This finding gave rise to the older term for this disorder, "tic douloureux."
- Trigger zones in the distribution of the affected nerve may be present; lightly touching these areas often triggers an attack. Other triggers include chewing, talking, brushing teeth, cold air, smiling, and shaving.

Investigations

- *Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA)* can identify demyelinating lesions, a mass lesion in the cerebellopontine angle, or an ectatic blood vessel which may be responsible for trigeminal neuralgia.
- These investigations are especially indicated for patients with sensory loss and young patients (under the age of 40).

Treatment

- *Medical therapy*—Pharmacologic therapy is the initial treatment for most patients with trigeminal neuralgia that is not caused by a structural lesion. Treatment consists of drugs such as carbamazepine, sodium valproate, phenytoin, baclofen, or clonazepam. Newer antiepileptic drugs such as gabapentin, lamotrigine, and topiramate are also effective. Patients who fail to respond to medication should be considered for microvascular decompression surgery.
- *Surgical therapy*—Surgery is reserved for patients who are refractory to medical therapy. A variety of surgical procedures may relieve symptoms in patients refractory to drug therapy. These include, microvascular decompression (involves the removal or separation of vascular structures, often an ectatic superior cerebellar artery, from the trigeminal nerve). Immediate postoperative relief is found in most patients. Percutaneous radiofrequency rhizotomy creates a lesion in the gasserian ganglion of the trigeminal nerve by application of heat. The lesion is thought to selectively destroy pain impulses carried by unmyelinated or thinly myelinated fibers.

Q. Glossopharyngeal neuralgia.

- Glossopharyngeal neuralgia is defined as paroxysmal pain in areas innervated by cranial nerves IX and X.

Etiology

- The usual cause of glossopharyngeal neuralgia appears to be microvascular compression, although abscess and tumor are sometimes associated.

Clinical Features

- The pain is paroxysmal, unilateral, sudden in onset, has a jabbing or briefly persistent quality.
- The pain is felt in or around the ear, tongue, jaw, or larynx and it can be triggered by chewing, swallowing, coughing, speaking, yawning, certain tastes, or touching the neck or external auditory canal.
- Many attacks may occur in a day and may awaken sufferers from sleep. Severe attacks have rarely been associated with bradycardia/asystole resulting in syncope presumably because of intense glossopharyngeal outflow and vagal efferent discharge.

Investigations

- MRI/MRA to rule out a mass lesion or vascular pathology.

Treatment

- Medical treatment is similar to that for trigeminal neuralgia and includes carbamazepine, gabapentin, or baclofen.
- Cases refractory to adequate medical treatment often respond to microvascular decompression.

Q. Postherpetic neuralgia (PHN).

- PHN refers to pain persisting beyond four months after an attack of herpes.

Clinical Features

- The probability of developing postherpetic neuralgia (PHN) increases with advanced age.
- The pain is described as "burning" by most patients with PHN. Most patients have allodynia, defined as pain evoked by nonpainful stimuli such as light touch.
- Patients often have areas of decreased sensation within the affected dermatomes.

Treatment

- There are many ways of treating postherpetic neuralgia: antidepressants (amitryptaline, nortryptaline), analgesics (aspirin, ibuprofen), capsaicin, topical anesthetics, anticonvulsants (carbamazepine, gabapentin), intrathecal corticosteroids, NMDA receptor antagonists (ketamine and dextromethorphan), cryotherapy, and surgery (anterolateral cordotomy, and electrocoagulation of the dorsal root).

Q. Describe the course of facial nerve. Enumerate the causes and clinical features of facial nerve palsy at various levels.

Facial nerve is a mixed nerve, but predominantly motor. It contains:

- Motor fibers to the facial muscles.
- Parasympathetic fibers to the lacrimal, submandibular, and sublingual salivary glands.
- Afferent fibers for taste from the anterior two-thirds of the tongue.
- Somatic afferents from the external auditory canal and pinna.

Course of Facial Nerve

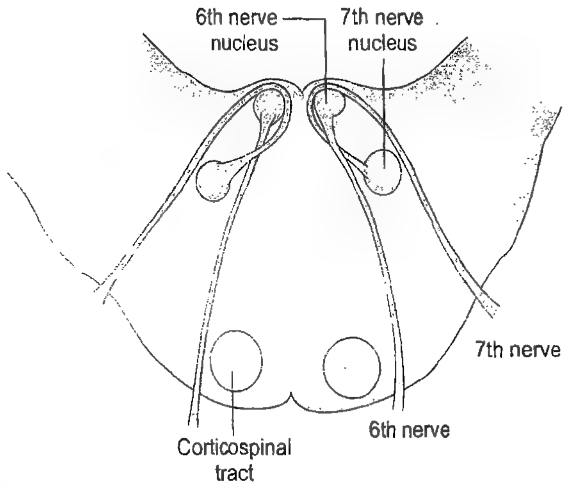

Fig. 5.3: Cross-section of pons showing origin of facial nerve

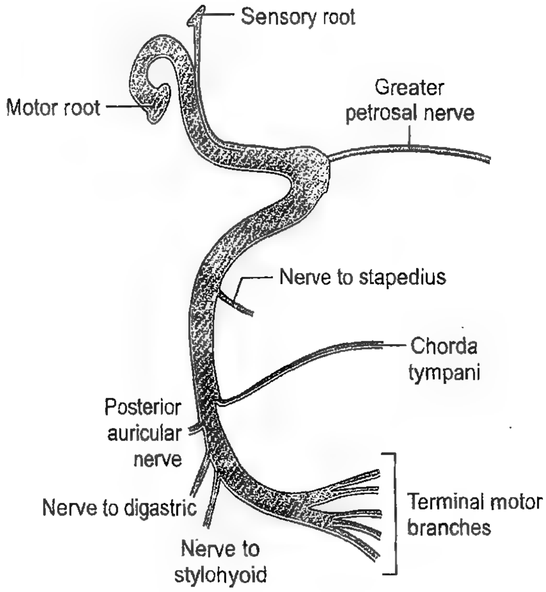

Fig. 5.4: Branches of facial nerve

- Facial nerve arises from its motor nucleus in the pons. The part of nucleus which supplies upper face has bilateral hemispheric representation. Hence, in unilateral UMN lesion of the facial nerve the upper part of the face is spared.
- Its fibers hook around the abducens nucleus (6th nerve) and then emerge from the lateral border of the pons.
- The nerve enters the internal auditory meatus along with eighth nerve and nervus intermedius.
- In the anterior part of inner ear, it bends downwards and anteriorly to enter facial canal.

Table 5.7 Clinical features of facial nerve lesions at various levels

Level	Causes	Clinical features
Supranuclear	Tumors, abscess, vascular events (infarction and hemorrhage)	Contralateral UMN facial palsy
At the level of pons (nucleus)	Pontine tumors (e.g. glioma), demyelination, vascular lesions (hemorrhage, infarct), poliomyelitis, motor neurone disease	Ipsilateral LMN facial palsy. Lesions in the pons also affect abduscent nerve producing lateral rectus palsy leading to convergent squint. Contralateral hemiparesis due to corticospinal tract involvement
At cerebellopontine angle (CPA)	Acoustic neuroma, meningioma and secondary neoplasm	Fifth, sixth, eighth and cerebellum are also affected with the seventh because all are close together in the CPA. Produces ipsilateral LMN facial palsy, sensorineural deafness, loss of corneal reflex, and ipsilateral cerebellar signs
At petrous temporal bone	Bell's palsy, trauma, middle ear infection, herpes zoster (Ramsay Hunt syndrome), and tumors (e.g. glomus tumor).	Ipsilateral LMN facial palsy, loss of taste on the anterior two-thirds of the tongue and hyperacusis (loud noise distortion due to paralysis of stapedius)
At the level of skull base and parotid gland	Paget's disease of bone, parotid gland tumors, mumps, sarcoidosis, trauma, and Guillain-Barré syndrome	Ipsilateral LMN facial palsy with intact taste sensation

- In the facial canal, it gives rise to greater petrosal nerve which supplies lacrimal glands and a branch to the stapedius muscle and is later joined by the chorda tympani nerve. During its course through the facial canal of temporal bone, the nerve is related to the labyrinth, the ossicles and the mastoid air cells.
- It leaves the temporal bone through the stylomastoid foramen and passes anteriorly through the parotid gland to divide into its peripheral branches.
- Facial nerve has a small sensory component. Taste sensation from anterior two-thirds of the tongue and sensory fibers from the external acoustic canal travel are supplied by facial nerve. The taste fibres run through the lingual nerve and then join the chorda tympani which in turn joins the facial nerve in the facial canal distal to the geniculate ganglion. Finally the tatse fibers enter the pons through the nervus intermedius to end in the nucleus tractus solitarius.

Clinical Features of LMN Facial Palsy

- Unilateral LMN lesion causes weakness of both upper and lower face on the same side of leison.
- Drooping of angle of mouth, dribbling of saliva from the angle of mouth, deviation of mouth to normal side.
- There is weakness of frowning (frontalis) and of eye closure since upper facial muscles are weak.
- Corneal exposure and ulceration may occur due to inability of the eyes to close during sleep.
- The platysma muscle is also weak.

Clinical Features of UMN Facial Palsy

- In UMN lesions only the lower part of face is affected and upper part is spared because of bilateral hemispheric representation. Hence, raising eyebrows, wrinkling of forehead, eye closure and blinking are all preserved.
- Clinical features in the lower part of the face are same as those described in LMN facial palsy.

Q. Discuss the etiology, clinical features, investigations and management of Bell's palsy.

- Bell's palsy is an acute, LMN type facial palsy.

Etiology

- Exact cause is unknown.
- It is thought to be due to a viral (often herpes simplex) infection that causes swelling of the nerve within the petrous temporal bone and stylomastoid foramen leading to compression of the nerve.

Clinical Features

- Patient notices sudden unilateral facial weakness.
- Weakness is LMN type (*see* above for clinical features of LMN facial palsy). Bell's phenomenon is uprolling of eyeballs when patient tries to close the eyes.
- Weakness progresses over hours or several days. Spontaneous recovery usually starts in the second week. Complete recovery may take 12 months.
- Some patients may be left with residual weakness.

Investigations

- *NCV studies*: Such as electromyograph (EMG) and motor nerve conduction studies can be used to assess the severity of lesion and chances of recovery.
- *Imaging studies*: Imaging is indicated if the physical signs are atypical, there is slow progression beyond three weeks, or if there is no improvement at six months. High resolution CT scanning and MRI can be used to rule out other causes of facial palsy such as tumors or vascular events. Pathological geniculate ganglion enhancement is seen in Bell's palsy.

Treatment

- Steroids (prednisolone 60 mg daily tapered over 10 days) with aciclovir have been shown to be more effective than either of these drugs alone.
- Eyes should be protected by applying artificial tears or tarsorrhapy (suturing the upper to lower eyelid).
- Facial nerve stimulation is useful within two weeks if surgical decompression is planned. Severe degeneration of the facial nerve is irreversible after two to three weeks.
- Surgical decompression of the facial nerve is not a currently recommended treatment. Decompression may be of benefit in patients with profound nerve dysfunction.

Q. Ramsay Hunt syndrome.

- Ramsay Hunt syndrome (RHS) was described by Ramsay Hunt in 1907. Herpes zoster oticus or cephalicus are the alternate names of this syndrome. RHS is a viral polyneuropathy, occurs after reactivation of varicella zoster virus (VZV) hiding inside dorsal roots and cranial nerve ganglions. Aging, malignancy, chemoradiotherapy exposure, immune deficiency may trigger reactivation of this virus.

Clinical Features

- Clinical features include a triad of ipsilateral LMN type facial palsy, ear pain, and vesicles in the auditory canal and auricle. Taste perception, hearing (tinnitus, hyperacusis), and lacrimation are affected in some

patients. Other cranial nerves V, IX, and X may also get involved. Vestibular disturbances (vertigo) may also be present.

Investigations

- Usually not necessary for the diagnosis. Viral serology with CSF examination may also be considered. Facial nerve functions can be measured with electrodiagnostic methods. Edema and inflammation of the facial nerve are detected with Gadolinium-contrast-MRI.

Treatment

- High dose steroids together with antiviral drugs (acyclovir, famciclovir, or valacyclovir) are used to treat RHS. The aim is to decrease the degeneration of the nerve. Intractable RHS cases resistant to medical therapy usually require surgical decompression of facial nerve.

Q. Draw a diagram showing various lobes of brain. Describe the functions and abnormalities of different lobes.

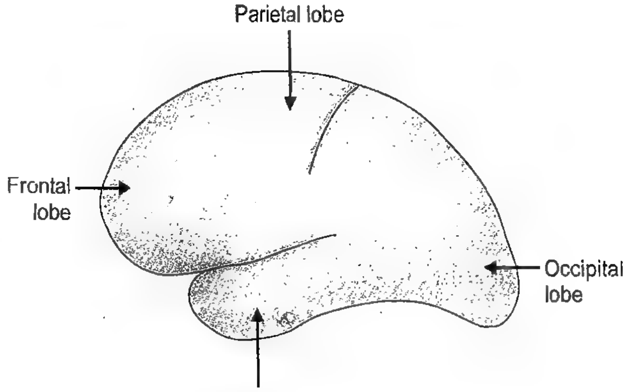

Fig. 5.5: Lobes of brain

Table 5.8 Normal and abnormal functions of the brain lobes

Lobe	Normal Function	Abnormal function due to lesions
Frontal lobe	Personality Emotional response Social behaviour	Disinhibition Obsessive-compulsive behavior Lack of initiative Antisocial behavior Impaired memory Incontinence Primitive reflexes (grasp reflex, snout reflex) Anosmia
Parietal lobe	***Dominant side*** Calculation Language Planned movement Steriognosis	Dyscalculia Dysphasia Dyslexia Apraxia Asteriognosis Homonymous hemianopia
	Non-dominant side Spatial orientation Constructional skills	Unilateral neglect Spatial disorientation Constructional apraxia Homonymous hemianopia
Temporal lobe	***Dominant side*** Auditory function Speech, language Verbal memory Olfaction	Dysphasia Dyslexia Poor memory Complex hallucinations (smell, vision) Homonymous hemianopia
	Non-dominant side Auditory function Music, tone sequences Non-verbal memory (faces, music, etc.) Olfaction	Poor non-verbal memory Loss of musical skills Complex hallucinations Homonymous hemianopia
Occipital lobe	Analysis of vision	Homonymous hemianopia Visual agnosia inability to recognize faces (prosopagnosia) Visual hallucinations (lights, zigzags)

Q. Define dementia. Enumerate the causes of dementia.

Q. Discuss the etiology, clinical features, investigations and management of dementia.

Or

Q. Discuss the etiology, clinical features, investigations and management of Alzheimer's disease.

- Dementia is defined as an acquired deterioration in cognitive abilities that impairs the performance of activities of daily living. Memory is the most common cognitive ability affected.

↓cognition (deterioration)

Causes of Dementia

Degenerative diseases
- Alzheimer's disease
- Dementia with Lewy bodies
- Frontotemporal dementia
- Huntington's disease
- Parkinson's disease

Structural brain problems
- Multi-infarct dementia
- Cerebral vasculitis
- Subdural hematoma
- Tumors
- Normal pressure hydrocephalus

Metabolic
- Uremia
- Liver failure

Toxic
- Alcohol
- Lead, mercury poisoning

Vitamin deficiency
- B_{12} deffeciency, thiamine deficiency, nicotinic acid (pellagra)

Traumatic
- Punch drunk syndrome (boxer's dementia)

Infections
- Creutzfeldt-Jakob disease
- HIV infection
- Neurosyphilis

Endocrine
- Hypothyroidism
- Hyperparathyroidsm
- Adrenal insufficiency
- Cushing's syndrome

- Degenerative diseases such as Alzheimer's disease cause progressive irreversible dementia.
- Some causes of dementias are reversible (reversible dementias). These are vit B_{12} deffeciency, thiamine deficiency, nicotinic acid deficiency (pellagra), hypothyroidism, chronic brain infections (syphilis, HIV) normal-pressure hydrocephalus, subdural hematoma, etc.

Alzheimer's Disease

- Alzheimer's disease is a progressive neurologic disorder which results in global cognitive impairement, personality changes, and functional impairments. It was first recognized by German psychiatrist Alois Alzheimer.
- Alzheimer's disease is the most common cause of dementia in the elderly. It accounts for 60 to 80% of dementias in the elderly. The disease is twice as common among women as among men, partly because women have a longer life expectancy.

Etiology and Pathogenesis

- Most cases are sporadic, with late onset (≥65 yr) and unclear etiology. However, about 5 to 15% of cases are familial (related to specific genetic mutations) and can have an early (presenile) onset (<65 yr).
- Healthy neurons have an internal support structure partly made up of structures called microtubules. These microtubules transport nutrients and molecules from the neuronal body to the ends of the axon and back. A special kind of protein, tau, binds to the microtubules and stabilizes them.
- In Alzheimer's disease, tau is changed chemically. It begins to pair with other threads of tau, to form neurofibrillary tangles. When this happens, the microtubules disintegrate, collapsing the neuron's transport system resulting in impaired communication between neurons and later death of the cells.
- At least 5 distinct genetic loci, located on chromosomes 1, 12, 14, 19, and 21, influence initiation and progression of Alzheimer disease. Mutations in genes for the amyloid precursor protein causes impaired processing of amyloid precursor protein, leading to deposition of β-amyloid. β-amyloid may lead to neuronal death and formation of neurofibrillary tangles and senile plaques, which consist of degenerated axonal or dendritic processes, astrocytes, and glial cells around an amyloid core.
- Other genetic determinants include the apolipoprotein (apo) E alleles. Apo E proteins influence β-amyloid deposition, cytoskeletal integrity, and efficiency of neuronal repair.
- The cholinergic system is involved in memory function, and cholinergic deficiency has been implicated in the cognitive decline and behavioral changes of Alzheimer's disease.

"↓Ach – Memory↓"

5

Clinical Features

- Patient presents with progressive memory loss and decline of other higher mental functions.
- Decline in language function manifests as difficulty in naming and understanding what others are speaking.
- Patient may also have apraxia (inability to carry out skilled motor activities), inability to recognize objects, places or people.
- There may be behavioral changes such as agitation, aggression, wandering and persecutory delusions, loss of insight and depression. Loss of inhibition may lead to inappropriate social behavior.
- In advanced stages, patients cannot walk, feed themselves, or do any other activities of daily living; they may become incontinent. Recent and remote memory is completely lost. Patients may be unable to swallow. They are at risk of undernutrition, pneumonia (especially due to aspiration), and pressure ulcers. At this stage, they are completely dependent on others and placement in a long-term care facility may be required. Additional clinical features may be present depending on the underlying cause.
- Mini-mental status examination (MMSE) helps to confirm the presence of cognitive impairment and to follow the progression of dementia. Neuropsychologic testing should be done when history and bedside mental status testing are not conclusive.
- In advanced stages, the person is mute, lies on bed and succumbs to intercurrent infections.

Investigations

Blood Tests

- Full blood count, ESR, urea and electrolytes, blood glucose, liver function tests, serum calcium, vitamin B_{12}, folate, thyroid function tests, HIV serology.

Imaging

- CT scan, MRI

"granulo-vacular"

Others

- EEG, CSF examination, brain biopsy

Management of Dementia

- Management is mainly supportive. Physical, mental and moral support should be provided to the patient by family members and care givers. The burden of illness falls frequently on family members.
- Treatment with antioxidants (mainly vitamin E) may help slow the decline of cognitive functions.
- The cholinesterase inhibitors donepezil, rivastigmine, and galantamine are somewhat effective in improving cognitive function. These drugs inhibit acetylcholinesterase, increasing the acetylcholine level in the brain.
- Memantine, an NMDA (N-methyl-D-aspartate) antagonist, may help slow the loss of cognitive function in patients with moderate to severe dementia and may be synergistic when used with a cholinesterase inhibitor. Ginkgo biloba, a plant extract has also been shown to be useful.
- Other drugs (e.g. antipsychotics) have been used to control behavior disorders. Patients with dementia and signs of depression should be treated with non-anticholinergic antidepressants, preferably SSRIs.
- Treatment of underlying cause.

Q. Define vertigo. Enumerate the causes of vertigo. Discuss the approach to a case of vertigo.

- Vertigo is a false sensation of movement of the self or the environment, usually a spinning or wheeling sensation. Almost everyone has experienced vertigo as the transient spinning dizziness immediately after turning around rapidly several times. Vertigo is a symptom, not a diagnosis.
- Dizziness is an imprecise term patients often use to describe various related sensations, including faintness (a feeling of impending syncope), light-headedness, feeling of imbalance or unsteadiness and a spinning sensation. So dizziness always does not mean vertigo.

Pathophysiology

- The vestibular system is the main neurologic system involved in balance. This system includes: the vestibular apparatus of the inner ear, the 8th (vestibulocochlear) cranial nerve, and the vestibular nuclei in the brainstem and cerebellum.
- Disorders of the inner ear and 8th cranial nerve are considered peripheral disorders. Those of the vestibular nuclei and their pathways in the brainstem and cerebellum are considered central disorders. Any asymmetrical neural activity anywhere in the vestibular system produces vertigo.

Etiology

Peripheral causes

- Benign paroxysmal positional vertigo (BPPV)
- Vestibular neuritis
- Herpes zoster oticus (Ramsay Hunt syndrome)
- Meniere's disease
- Labyrinthine concussion
- Perilymphatic fistula
- Acoustic neuroma
- Aminoglycoside toxicity
- Otitis media

Central causes
- Migrainous vertigo
- Brainstem ischemia
- Cerebellar infarction and hemorrhage
- Chiari malformation
- Multiple sclerosis

Others
- Drugs (anticonvulsants, alcohol)

Approach to a Case of Vertigo

Clinical History and Findings

- Peripheral vertigo should be distinguished from central vertigo, because central vertigo is of more serious nature.
- Ask the patient to describe what exactly he feels. This will help in differenciating true vertigo from other causes of dizziness such as lightheadedness.
- Nausea, vomiting and imbalance usually accompanies vertigo.
- H/o recurrent episodes in the past suggest BPPV.
- Ask about triggers and relievers, i.e. whether triggered by head/body position change which suggests peripheral vertigo.
- Tinnitus and hearing loss suggest middle ear pathology and vertigo of peripheral origin.
- Presence of nystagmus should be noted. In peripheral lesions, nystagmus is usually horizontal with a rotatory component. In central vertigo, nystagmus is usually vertical and may be associated with other signs of brain stem or cerebellar dysfunction.
- H/o of loss of consciousness, focal neurological findings and cerebellar signs suggests a central cause of vertigo.

Investigations

- Audiologic tests, caloric stimulation, electronystagmography, CT scan or MRI, and brainstem auditory evoked potential studies are indicated in patients with persistent vertigo or when CNS disease is suspected.
- These studies will help distinguish between central and peripheral lesions and to identify causes requiring specific therapy.

Treatment

Symptomatic Treatment

- These medications can be used to suppress the vertigo whatever may be the cause. These drugs act by suppressing the vestibular system. Examples are scopolamine, cinnarizine, betahistine, meclozine, dimenhydrinate, diphenhydramine, prochlorperazine, promethazine, metoclopramide, and domperidone.

Disease Specific Treatment

- If any underlying disease is found, treatment should be directed towards that.

Q. Nystagmus.

- Nystagmus is involuntary rhythmic oscillation of the eyes. Due to the involuntary movement of the eye, it is often called "dancing eyes".
- Nystagmus can be horizontal, vertical, torsional or a combination of these. Nystagmus may be unilateral or bilateral, conjugate or disconjugate (dissociated), congenital or acquired.

Pathophysiology

- Eyes move reflexively to adjust for slight movement of head, which stabilizes the image that we are looking at and allows us to see a sharper image. Nervous system maintains position of the eyes by three mechanisms: eye fixation, the vestibulo-ocular reflex, and the neural integrator. Any abnormality in these three mechanisms stimulating the eye movements in the absence of head movement causes nystagmus.

Table 5.9 Differences between peripheral and central vertigo

Feature	Peripheral vertigo	Central vertigo
Nystagmus	Combined horizontal and torsional; inhibited by fixation of eyes onto object; fades after a few days	Purely vertical, horizontal, or torsional; not inhibited by fixation of eyes onto object; may last weeks to months
Imbalance	Mild to moderate; able to walk	Severe; unable to stand still or walk
Nausea, vomiting	May be severe	Varies
Hearing loss, tinnitus	Common	Rare
Neurologic deficits	Rare	Common
Latency following provocative maneuver	Longer (up to 20 seconds)	Shorter (up to 5 seconds)

Causes of Nystagmus

- ***Congenital***: Albinism, bilateral congenital cataract, optic nerve hypoplasia, Noonan syndrome
- ***Acquired***: Benign paroxysmal positional vertigo, brain tumors in the posterior fossa, lateral medullary syndrome, Méniére's disease, Wernicke-Korsakoff syndrome, cerebellar ataxia, alcohol intoxication, phenytoin.

Clinical Features

- The primary symptom of nystagmus is involuntary eye movement. Usually the movement is side-to-side (horizontal nystagmus), but it can also be up and down (vertical nystagmus) or circular (torsional or rotary nystagmus).
- The oscillations may be sinusoidal and of approximately equal amplitude and velocity (pendular nystagmus) or, more commonly, with a slow initiating phase and a fast corrective phase (jerk nystagmus).
- Vertigo usually accompanies nystagmus due to peripheral vestibular disease.
- Oscillopsia (a to-and-fro illusion of environmental motion) and blurred vision occur due to oscillation of retinal image.
- There may be abnormal head position because the patient tends to keep their head in a position which causes least oscillopsia or blurred vision.

Investigations

- Brain imaging (CT or MRI) to rule out any brain pathology.
- Electronystagmographs record eye muscle contractions to evaluate the direction and velocity of nystagmus. It may be used to evaluate low-amplitude nystagmus.

Treatment

- Treatment of underlying cause.
- *Medications*—baclofen and gabapentin may reduce nystagmus.
- *Botulinum injections*—this has been used to weaken the extraocular muscles and diminish the amplitude of nystagmus.
- *Prism lenses—and optical solutions*. These can be used to keep the eyes in a position of gaze in which nystagmus is minimal.
- *Surgery*—attachment of the muscles is shifted to maintain a gaze position where nystagmus is minimal or absent.

Q. Discuss the causes, clinical features and management of raised ICP (intracranial pressure).

- Intracranial pressure is normally 7 to 15 mmHg in adults. If pressure is more than 20 mm Hg, it is called raised ICP.

Mechanisms of Raised ICP

- The volume of brain parenchyma is relatively constant in adults. The volumes of CSF and blood in the intracranial space are variable. Any abnormal increases in the volume of any of these components may lead to elevation in ICP.
- CSF is produced by the choroid plexus at a rate of 20 ml/h (500 ml/day). CSF is reabsorbed via the arachnoid granulations into the venous system. Increased production or decreased absorption of CSF can lead to raised ICP.
- Cerebral blood flow increases with hypercapnia and hypoxia and may lead to raised ICP.

Causes of Raised ICP

- Intracranial hemorrhage
- Central nervous system infections
- Space occupying liesion (neoplasm, abscess, hematoma)
- Vasculitis
- Ischemic infarcts with cerebral edema
- Obstructive hydrocephalus
- Cortical venous sinus thrombosis
- Pseudotumor cerebri
- Idiopathic

Clinical Features

- Symptoms of elevated ICP include headache, depressed consciousness and vomiting.
- Signs include 6th nerve palsies, papilledema, and a triad of bradycardia, respiratory depression, and hypertension (Cushing's triad, sometimes called Cushing's reflex or Cushing's response). Cushing's triad may be due to brainstem compression. The presence of this response is an ominous finding that requires urgent intervention.
- Signs and symptoms of underlying disease.

Management

- *Head end elevation*: It increases venous return from head and lowers ICP.
- *Hyperventilation*: It decreases $PaCO_2$ and causes cerebral vasoconstriction which decreases the volume of intracranial blood and thus reduces raised ICP
- *Intravenous mannitol*: This is an osmotic diuretic. It reduces brain volume by drawing free water out of the tissue into the circulation, where it is excreted by the kidneys, thus dehydrating brain parenchyma. Dose is 1 to 1.5 g/kg of 20% mannitol every six to eight hours.

- *Corticosteroids*: Dexamethasone 4 mg 6th hourly is used in raised ICP due to meningitis and brain tumours.
- *Glycerol*: 30 ml orally every 6th to 8th hourly
- *Barbiturates*: It reduces brain metabolism and cerebral blood flow, thus lowering ICP and exerting a neuro-protective effect. Pentobarbital is generally used, with a loading dose of 5 to 20 mg/kg as a bolus, followed by 1 to 4 mg/kg per hr.
- *Therapeutic hypothermia*: Hypothermia decreases cerebral metabolism and may reduce cerebral blood flow and ICP.
- *Removal of CSF*: Removal of CSF reduses ICP which can be done by ventriculostomy.
- *Decompressive craniectomy*: Removal of the rigid confines of the bony skull allows the intracranial contents to expand and reduces ICP.
- *Specific treatment*: The best treatment of elevated ICP is to correct the underlying cause. Examples are removal of meningioma or intracranial hematoma.

Q. Classify and enumerate the causes of meningitis.

- Meningitis is an inflammatory disease of the arachnoid mater and the cerebrospinal fluid.

Table 5.10 Causes of meningitis

Bacteria
- *Neisseria meningitidis*
- *Streptococcus pneumoniae*
- *H. influenzae*
- *Mycobacterium tuberculosis*
- *Staphylococcus aureus*
- *Group B Streptococcus*
- *Listeria monocytogenes*
- *Treponema pallidum*

Viruses
- Enteroviruses
- ECHO
- Coxsackie
- Mumps
- Herpes simplex
- HIV
- Epstein-Barr virus

Fungi
- *Cryptococcus neoformans*
- Candida
- *Coccidioides immitis*
- *Histoplasma capsulatum*

Spirochetal
- Leptospirosis
- Lyme disease
- Syphilis

Rickettsial
- Typhus fever

Protozoal
- Naegleria

Miscellaneous
- Sarcoidosis
- Leukemic meningitis
- Chemical meningitis
- Drug induced—NSAIDs, rofecoxib, intravenous immunoglobulin.

Q. Describe the etiology, clinical features, investigations and management of acute pyogenic meningitis (acute bacterial meningitis).

Q. Causes of neck stiffness.

Q. Kernig's sign; Brudginski's sign.

Q. Prevention of meningitis.

Etiology

Common Organisms

- *Neisseria meningitidis* --- adolesent
- *Streptococcus pneumoniae*.... elder/adults
- *H. influenzae* ... (1m – 2yrs)

Uncommon Organisms

- *Staphylococcus aureus*
- Group B streptococcus → world (<1m)
- *Listeria monocytogenes* KEL--(<1m)
- Klebsiella
- Proteus
- Pseudomonas
- Salmonella
- *Neisseria gonorrhea*

Pathogenesis

- The organism responsible for meningitis can reach the CSF via three routes: (1) colonization of the nasopharynx with subsequent bloodstream invasion and subsequent central nervous system (CNS) invasion, (2) invasion of the CNS following bacteremia due to a localized source, such as pneumonia, infective endocarditis or a urinary tract infection, (3) direct entry of organisms into the CNS from a contiguous infection (e.g. sinuses, mastoid), trauma, or neurosurgery.
- There are many steps involved before frank meningitis develops such as colonization of the host mucosal epithelium by pathogens, invasion into bloodstream, crossing of the blood–brain barrier, and multiplication within the CSF.
- Much of the damage from meningitis results from cytokines (interleukin-1, interleukin-6, and tumor necrosis factor-alpha) released within the CSF due to inflammatory response. Once inflammation is initiated, a series of injuries occur to the endothelium of the blood–brain barrier (e.g. separation of intercellular tight junctions) that result in vasogenic brain edema, loss of cerebrovascular autoregulation, and increased intra-cranial pressure. This results in localized areas of brain

ischemia, cytotoxic injury, and neuronal apoptosis. All these pathologic changes manifest clinically as coma, seizures, deafness, and motor, sensory, and cognitive deficits.

Predisposing Factors

- *Immunodeficient states*: Asplenism, complement deficiency, corticosteroid excess, diabetes mellitus, chronic alcoholism and HIV infection.
- Acute otitis media.
- Recent exposure to someone with meningitis.
- Recent travel, particularly to areas with endemic meningococcal disease.
- Injection drug use.
- Recent head trauma with CSF otorrhea or rhinorrhea.

Clinical Features

- Patients with bacterial meningitis usually appear ill. The classic triad of acute bacterial meningitis consists of fever, nuchal rigidity, and a change in mental status. "fever"
- Patients are usually febrile but some may have hypothermia.
- Headache is also common and is diffuse and severe.
- *Neck stiffness*: Spasm of neck muscles on attempted flexion.
- *Brudzinski's neck sign*: Passive neck flexion, while the patient is in supine position, produces involuntary flexion of hips and knees.
- *Brudzinski's leg sign*: Passive flexion of one leg produces automatic flexion of the other leg.
- (k–k) *Kernig's sign*: Extension of knee from flexed thigh position causes passive resistance. This is due to the spasm of hamstring muscles due to the inflamed sciatic nerve as it passes through the spinal theca.
- Other manifestations include photophobia, seizures, focal neurologic deficits (including cranial nerve palsies), and papilledema. → ICT
- Certain bacteria, particularly *N. meningitidis*, can cause characteristic skin manifestations, such as petechiae and palpable purpura.
- Arthritis occurs in some patients with bacterial meningitis.

Investigations

- *Blood counts*: White blood cell count is often elevated with a let shift. However there may be leucopenia in severe infection. Platelet count may be reduced if disseminated intravascular coagulation (DIC) is present or in the face of meningococcal bacteremia.
- *Blood cultures*: Blood cultures may be able to identify the causative organism in 50 to 75 percent of patients with bacterial meningitis.
- * *Serum procalcitonin* levels can be used as a guide to distinguish between bacterial and aseptic meningitis in children. Elevated serum procalcitonin levels predict bacterial meningitis.
- *Lumbar puncture and CSF analysis*: This is the test of choice to diagnose meningitis. Every patient with suspected meningitis should have LP done unless the procedure is contraindicated. CSF should be sent for protein, sugar, cell count, cell type, Gram's stain, India ink stain, culture sensitivity, AFB stain and culture and PCR studies. Opening pressure should be noted at the time of LP → SAH
- *CT scan head*: A contrast CT shows meningeal enhancement in meningitis. It is also helpful to rule out other pathologies such as subarachnoid hemorrhage, cerebral abcess, mass lesion, middle ear and sinus disease. It should be done before LP in patients with raised ICP or mass lesion to prevent the risk of herniation. CT scan before an LP is indicated in patients with one or more of the following risk factors for a mass lesion.

Indications for CT Scan before LP in Meningitis

- Immunocompromised state (e.g. HIV infection, immunosuppressive therapy)
- History of CNS disease (mass lesion, stroke, or focal infection)
- New onset seizure (within one week of presentation)
- Papilledema
- Abnormal level of consciousness
- Focal neurologic deficit.

Table 5.11 CSF findings in meningitis of different etiology

	Normal	Viral	Pyogenic	Tuberculosis
Appearance	Crystal-clear	Clear/turbid	Turbid/purulent	Turbid/viscous
Pressure	60 to 200 mm of CSF	Normal	Increased	Increased
WBC count	<5/mm³, all lymphocytes	10–300/mm³ lymphocyte predominant	100–5000; >80% neutrophils	100–500/mm³, most are lymphocytes
Protein	less than 50 mg/dl	Increased	Increased ↑↑	Increased >100 ↑↑↑
Glucose	40–60% of blood glucose	Normal	Low ↓↓↓	Low ↓ ↓↓↓

5

Treatment

- Bacterial meningitis is a medical emergency and treatment should be initiated immediately as soon as it is suspected. The mortality rate of untreated disease approaches 100 percent.
- There are two general principles of antibiotic therapy: use of bactericidal drugs effective against the infecting organism; and the use of drugs that enter the CSF, since the blood–brain barrier prevents macromolecule entry into the CSF.

Empiric Antibiotic Therapy

- Pending identification of the causative organism, empric antibiotic therapy should be started.
- Third-generation cephalosporins, such as cefotaxime and ceftriaxone, are the drugs of choice for this purpose because they have good CSF penetration and also good activity against pathogens. These drugs have potent activity against the major pathogens of bacterial meningitis with the exception of *Listeria monocytogenes*.
- Empiric therapy can be chosen based on the common organism causing meningitis in different age groups.
- Ampicillin can be added to cover for *Listeria monocytogenes* in elderly. Many doctors add vancomycin also to cover for penicillin-resistant pneumococci.

Table 5.12 Empirical antibiotic therapy for acute pyogenic meningitis

Age range	Common organisms (in decreasing frequency)	Empirical antibiotics
Neonates and infants	*E. coli* Group B Streptococcus "GBS-strep" *L. monocytogenes* KEL *S. pneumoniae*	Ampicillin plus cefotaxime or ceftriaxone "listeria" "Penicillin"
Children <12 years	*N. meningitidis* -ve *S. pneumoniae* +ve *H. influenzae*	Ceftriaxone (or cefotaxome) plus vancomycin Strept pneumo
Adults up to age 60	*S. pneumoniae* *N. meningitidis* + listeria *H. influenzae* Group B streptococcus	Ceftriaxone (or cefotaxome) plus vancomycin
elderly		
Above 60 years	*S. pneumoniae* *L. monocytogenes* *N. meningitidis* Group B streptococcus *H. influenzae*	Ampicillin plus ceftriaxone (or cefotaxime) plus vancomycin

Organism Specific Antbiotic Therapy

2gm BID I/V – 14days

Table 5.13 Organism specific antbiotic therapy in acute pyogenic meningitis 1gm BID I/V x 14days

S. pneumoniae	Ceftriaxone (2 g Q 12 h) plus vancomycin (500 mg Q 6 h) for 14 days; vancomycin can be discontinued if the isolate is not cephalosporin-resistant
N. meningitidis → 7days, Group B streptococci	Penicillin G (4 million units Q 4 h) for seven days in case of *N. meningitidis* and for two to three weeks in case of Group B streptococci
H. influenzae, Enterobacteriaceae	Ceftriaxone (2 g Q 12 h) or cefotaxime (2 g Q 6 h) for seven days for *H. influenzae* Above plus gentamicin (1–2 mg/kg Q 8 h) for three weeks for Enterobacteriaceae
>60yrs *L. monocytogenes*	Ampicillin (2 g Q 4 h) or penicillin G (3–4 million U Q 4 h) plus gentamicin (1–2 mg/kg Q 8 h) for two to four weeks
Pseudomonas or acinetobacter	Ceftazidime (2 g Q 8 h) plus gentamicin (1–2 mg/kg Q 8 h) for three weeks

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Role of Steroids in Meningitis

- Trials have shown that dexamethasone given shortly before or at the same time as the first dose of antibiotics significantly improves outcomes in patients with meningitis.
- Dexamethasone reduces CSF synthesis of cytokines (such as tumor necrosis factor-alpha and interleukin-1), CSF inflammation, and cerebral edema which are responsible for much of the damage and sequelae.

Complications of Meningitis

Neurological

- Cerebrovascular abnormalities (thrombosis, vasculitis, hemorrhage, and aneurysm formation)
- Cerebral edema and raised ICP
- Obstructive hydrocephalus
- Seizures
- Intellectual impairment
- Deafness and cranial nerve palsies
- Subdural abscess.

Systemic

- Septic shock
- ARDS
- DIC

Prevention of Meningitis

- Some forms of meningitis can be prevented by vaccination and chemoprophylaxis.

Vaccines

- Vaccines are available for *S. pneumoniae, N. meningitidis*, and *H. influenzae*.
- Pneumococcal vaccine—Pneumococcal vaccine is administered to chronically ill and older adults (over age 65). Pneumococcal vaccine is administered intramuscularly as a 0.5 ml dose. Effect lasts up to 5–10 years.
- Meningococcal vaccine—A quadrivalent meningococcal polysaccharide conjugate vaccine (serogroups A, C, Y and W-135) is available in many countries. It is given to children and adults as a single intramuscular (IM) 0.5 ml dose. Effect lasts up to 1 year.
- *H. influenzae* vaccine—this vaccine is now routinely administered to children. It is available in combination with hepatitis B vaccine. For adults, it is indicated only for those with prior splenectomy.

Chemoprophylaxis

- Chemoprophylaxis can prevent the spread of meningococcal and *Haemophilus meningitis*.
- *Neisseria meningitides*: Rifampicin (600 mg PO every 12 h for a total of four doses in adults), or ciprofloxacin (500 mg PO once), or ceftriaxone (250 mg IM once). Chemoprophylaxis is necessary only in close contacts of an isolated case of invasive meningococcal infection. Close contacts include household members and other intimate contacts, children in school environments, coworkers in the same office, young adults in dormitories, and recruits in training centers.
- *H. influenza*: Unvaccinated, young children (less than four years of age) should receive brief course of rifampicin (20 mg/kg with a maximum of 600 mg/day PO for four days) if they are exposed to a case of meningitis.

Q. Aseptic meningitis.

- Aseptic meningitis refers to patients who have clinical and laboratory evidence for meningeal inflammation with negative routine bacterial cultures.
- Causes of aseptic meningitis are viruses (most common cause is enterovirus), infections due to fungi and spirochetes, drugs (NSAIDs, rofecoxib, carbamazepine, ciprofloxacin, isoniazid), malignancy, sarcoidosis and Behçet's disease.
- Clinical features are similar to bacterial meningitis (e.g. fever, headache, altered mental status, stiff neck, photophobia).
- CSF show increased pressure and lymphocytic pleocytosis. CSF protein and sugar are usually normal.
- Treatment involves correction of the underlying cause. However, in contrast to bacterial meningitis, majority of patients with aseptic meningitis have a self-limited course that will resolve without specific therapy.

Q. Describe the etiology, clinical features, investigations and management of tuberculous meningitis (TBM).

Etiology

- *Mycobacterium tuberculosis*.

Pathophysiology

- TBM develops in 2 steps. In the first step *Mycobacterium tuberculosis* bacilli enter the host by droplet inhalation, and are phagocytosed by alveolar macrophages. Subsequently bacilli spread to regional lymph nodes to produce the primary complex. During this stage, bacteremia occurs and the tubercle bacilli seed many organs. In persons who develop TBM, bacilli seed to the meninges or brain parenchyma, resulting in the formation

of subpial or subependymal foci of caseous lesions. These are termed Rich foci, after the original pathologic studies of Rich.

- The second step in the development of TBM is an increase in size of a Rich focus until it ruptures into the subarachnoid space. Tubercles (Rich focus) rupturing into the subarachnoid space cause meningitis. Those deeper in the brain or spinal cord parenchyma cause tuberculomas or abscesses. A severe inflammatory response is elicited by mycobacterial components. A thick exudate, phlebitis, arteritis, thrombosis, infarction and obstruction of CSF flow are common findings. Basal meningitis accounts for the frequent dysfunction of cranial nerves (CNs) III, VI, and VII, eventually leading to obstructive hydrocephalus from obstruction of basilar cisterns. Complications include raised intracranial pressure, cerebral edema, syndrome of inappropriate antidiuretic hormone SIADH secretion, hydrocephalus, brain infarcts, hemi- or quadriplegia, convulsions, deafness, blindness, mental retardation and other neurological sequelae.

Clinical Features

- TBM presents as a subacute febrile illness which may progress through 3 phases.
- *Prodromal phase*: Lasts 2 to 3 weeks. There is insidious onset of malaise, lassitude, headache, low-grade fever, and personality change.
- *Meningitic phase*: Characterized by signs of meningeal irritation, headache, vomiting, lethargy, confusion, and cranial nerve palsies.
- *Paralytic phase*: Confusion progresses to stupor and coma. Seizures and hemiparesis can occur.
- Fundoscopic examination often shows choroidal tubercles.
- If untreated, death occurs within five to eight weeks of the onset of illness.

Diagnosis

- *CSF examination*: CSF shows elevated protein and decreased glucose concentration with predominant lymphocytosis. The demonstration of acid-fast bacilli (AFB) in the CSF remains the most rapid and effective means of reaching an early diagnosis. PCR for AFB should be sent in all suspectd cases of TB meningitis.
- *Brain imaging*: CT scan head, may show meningeal enhancements especially basal meninges. Obstructive hydrocephalus may be present. MRI has more sensitivity in detecting the distribution of meningeal inflammatory exudates.
- *Montoux test* is usually positive.
- *Chest X-ray*: May show evidence of pulmonary tuberculosis.
- *Other tests*: HIV test to rule out immunocomromised state, blood sugar, electrolytes, LFT, RFT, and CBP with ESR.

Treatment

- Antituberculous therapy should be started if there is strong clinical suspicion of TB meningitis even if it cannot be confirmed by investigations.
- Treatment involves initial two month period of intensive therapy, with 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol. This is followed by a continuation phase lasting seven to 10 months, with 2 drugs (isoniazid, rifampicin).
- Steroids should be given to all patients with TB meningitis. Dexamethasone is given at a dose of 12 mg/day in divided doses or prednisolone at a dose of 60 mg/day. Steroids should be given in full dose for 3 weeks, and then tapered off gradually over the following 3 weeks.
- *Surgery*: Patients with hydrocephalus may require surgical decompression to reduce raised intracranial pressure.

Q. Define stroke.

Q. What are the types of sroke (cerebrovascular accident)?

Q. Enumerate the risk factors for stroke.

- Stroke or cerebrovascular accident (CVA) is defined as sudden onset of a neurologic deficit from a vascular mechanism.
- Stroke is the leading cause of neurologic disability in adults. It is more common in males and mainly affects elderly people. Blacks have almost twice the risk of stroke compared to whites.

Types

- *Ischemic*: 85% of strokes are ischemic
- *Hemorrhagic*: 15% are hemorrhagic strokes, further classified as subarachnoid hemorrhage and intracerebral hemorrhage

Risk Factors for Stroke

Hypertension — ICH
Diabetes
Smoking
Alcohol consumption
Family history of stroke
Obesity
Hyperlipidemia
Trauma (hemorrhagic stroke)
Drug use, especially cocaine and amphetamines
Male sex
Older age
Race or ethnic background (e.g. blacks and Mexican Americans)

Hypercoagulable disorders

Q. Discuss the etiology, risk factors, clinical features, investigations and management of ischemic stroke.

Etiology

- Ischemic stroke is due to sudden occlusion of an intracranial vessel, with reduction in blood flow to the brain area supplied by that vessel. Occlusion happens either due to in situ thrombosis or embolus from a distant site.
- In-situ thrombosis can happen in a previously diseased vessel such as atheroscleorotic vessels. Rupture of an atherosclerotic plaque or acute dissection of a large vessel (e.g. internal carotid artery, middle cerebral artery) can also lead to acute thrombosis.
- Emboli can come from distant sites and occlude cerebral vessels. Sources of emboli include heart and other arteries (e.g. the internal carotid and aortic arch).
- The causes listed under "cardioembolic and uncommon causes" produce stroke in young (<50 years) also.

Pathophysiology of Ischemic Stroke

- Acute occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies. Reduction of blood supply produces ischemia or infarction depending on the severity of reduction of blood flow.
- If blood flow is restored before significant amount of cell death, patient may experience only transient symptoms, i.e. a TIA.
- The infarcted area is surrounded by ischemic area the function of which is reversible if blood flow is restored within a reasonable time. This area is called *ischemic penumbra*. The ischemic penumbra will eventually infarct if blood flow is not restored. Saving the ischemic penumbra is the goal of revascularization therapies.
- Cerebral infarction occurs via two pathways: (1) cellular necrosis and (2) apoptosis in which cells become programmed to die.
- Cellular necrosis happens due to severe reduction in blood supply which results in failure of mitochondria to produce ATP. Loss of ATP production leads to stoppage of membrane ion pumps allowing calcium to accumulate inside cells and glutamate release from synaptic terminals. Excess glutamate also leads to intracellular calcium accumulation. Excess calcium inside neurons produces free radicals by membrane degradation and mitochondrial dysfunction. Free radicals ultimately lead to death of neuronal cells.
- In apoptosis, cells die days to weeks later. It is seen in ischemic penumbra.

Clinical Features of Ischemic Stroke

- Initial symptoms occur suddenly. Generally, they include numbness, weakness, or paralysis of the contralateral limbs and the face, inability to speak (aphasia); confusion; visual disturbances in one or both eyes; dizziness or loss of balance and coordination; and headache.

Table 5.14 Causes of ischemic stroke

Common causes	Uncommon causes
Thrombosis • Small vessel thrombosis (lacunar stroke) • Large vessel thrombosis • Dehydration *Embolic occlusion* • Artery-to-artery mc – Carotid disease – carotid artery bifurcation – Aortic disease • Cardioembolic ---> MCA/PCA >> A.C.A. – Atrial fibrillation – Mural thrombus – Myocardial infarction – Dilated cardiomyopathy – Valvular lesions (mitral stenosis, mechanical valve) – Infective endocarditis – Paradoxical embolus (ASD, patent foramen ovale)	• Hypercoagulable disorders – Protein C deficiency – Protein S deficiency – Antithrombin III deficiency – Antiphospholipid syndrome – Factor V Leiden mutation – Malignancy – Sickle cell anemia – Polycythemia vera – Essential thrombocytosis – Homocysteinemia – Nephrotic syndrome • Venous sinous thrombosis • Fibromuscular dysplasia • Vasculitis (PAN, Wegener, Takayasu, giant cell arteritis, syphilis, tuberculosis) • Atrial myxoma • Drugs: Cocaine, amphetamine • Moyamoya disease

Table 5.15 Clinical features of ischemic stroke

Occluded blood vessel	Clinical manifestations
Internal carotid artery * blindness * MCA	Ipsilateral blindness (variable) and features of MCA territory stroke
Middle cerebral artery (MCA) · Motor ⊕ – arm & face · sensory · hemianopia · aphasia (Dom^nt) · apraxia	Contralateral hemiparesis (worse in the arm and face than in the leg), dysarthria, hemianesthesia, contralateral homonymous hemianopia, aphasia (if the dominant hemisphere is affected) or apraxia and sensory neglect (if the nondominant hemisphere is affected)
Anterior cerebral artery (ACA) · Motor – leg. · Incontinence · gait apraxia.	Contralateral hemiparesis (worse in the leg than arm), urinary incontinence, apathy, confusion, poor judgment, mutism, grasp reflex, gait apraxia
Posterior cerebral artery (PCA) * 3rd CN palsy. * Memory.	Contralateral homonymous hemianopia, unilateral cortical blindness, memory impairment, unilateral 3rd cranial nerve palsy, hemiballismus
Vertebrobasilar system ↓ brainstem ⊕	Unilateral or bilateral cranial nerve deficits (producing nystagmus, vertigo, dysphagia, dysarthria, diplopia, blindness), truncal or limb ataxia, spastic paresis, crossed sensory and motor deficits, impaired consciousness, coma, death (if basilar artery occlusion is complete), tachycardia, labile BP

- Systemic or autonomic disturbances (e.g. hypertension, fever) occasionally occur.
- H/o sudden, severe headache, vomiting, impaired consciousness or coma suggests intracranial bleed.
- Neurologic deficits depend on the vessel blocked and the area of brain involved (*see* Table 5.15).

Investigations

CT Scan Head

- Plain CT head is the imaging modality of choice in acute stroke because it can be done fast and is widely available. An infarct appears as hypointense area. However, infarct may not be visible for 24–48 hours in CT scan. Brainstem lesions may not appear properly on CT scan.
- CT scan can also exlude hemorrhage, and other pathologies like neoplasms, abscesses, and other conditions that mimic stroke.
- Contrast-CT is more useful in subacute infarcts and can also visualize venous structures.

MRI Brain

- MRI is less sensitive in excluding hemorrhage than CT. It is also more expensive and time consuming, less available, and limited by claustrophobia. Because of all these reasons, MRI is not preffered in the acute evaluation of stroke.
- However, MRI is more sensitive than CT in picking up infarction in all areas of the brain, including cortex and brainstem.
- It is more sensitive in picking up early brain infarction than CT scan.

CT-angiogram and MR-angiogram

- Can be done to identify the exact location of vessel block.

Carotid and Vertebral Artery Doppler

- Useful to identify diseases of the carotid and vertebral arteries.

ECG and Echocardiogram

- To rule out any heart problem.

Blood Tests

- Blood sugar, urea, creatinine, electrolytes, hemoglobin, cell count, coagulation parameters, lipid profile, toxicology screen (if toxin or overdose suspected).

Treatment

Initial Management

- Assess ABCs (airway, breathing, circulations).
- Secure airway.
- Monitor oxygenation.
- Provide respiratory ventilatory support if required.

Antithrombotic Treatment

- Antiplatelet agent, aspirin should be given as soon as the diagnosis of ischemic stroke is confirmed. A loading dose of asprin 325 mg should be given followed by 150 mg daily lifelong. Aspirin prevents the extension of clot and also reduces the chances of recurrent stroke (secondary prevention). However, withhold these agents before and for 24 hours after thrombolytic therapy.
- Clopidogrel is not useful in the acute management of stroke, but can be given along with aspirin to patients at high risk of developing subsequent ischemic stroke (especially patients with coexisting ischemic heart disease)

Anticoagulations

- They are not useful in atherothrombotic cerebral ischemia. However, they are indicated in cardioemblic stroke (e.g. in atrial fibrillation). Heparin or low-molecular-weight heparin can be given subcutaneously and later changed to oral anticoagulant therapy with warfarin.

Intravenous Thrombolysis

- Recombinant tPA (tissue plasminogen activator) has been shown to improve the outcome if given within 3 hours after the onset of stroke. There is a slighltly increased risk of intracranial bleed especially if given after 3 hours. tPA is contraindicated in the presence of high BP (>185/110), recent major surgery, prior stroke or head injury within 3 months and gastrointestinal bleeding in preceding 3 weeks.

Endovascular Techniques

- These techniques include intra-arterial thrombolysis and endovascular thrombectomy. They can be used in ischemic stroke due to large-vessel occlusions such as middle cerebral artery (MCA), internal carotid artery, and the basilar artery.

Supportive Meausures

- Prevent infections (pneumonia, urinary tract, and skin) and deep venous thrombosis (DVT).
- Fever is detrimental and should be treated with antipyretics and surface cooling.
- Blood glucose should be monitored and kept at <110 mg/dL.
- Patients may develop cerebral edema which causes obtundation or brain herniation. Edema peaks on the second or third day. It is likely to develop in large infarcts. It should be reduced by IV mannitol and head end elevation.

Rehabilitation

- Rehabilitation services improve neurologic outcomes. Proper rehabilitation of the stroke patient includes early physical, occupational, and speech therapy. The goal of rehabilitation is to return the patient to home and to maximize recovery by providing a safe, progressive regimen suited to the individual patient.

Q. Lacunar infarcts (lacunar stroke).

- Lacunar infarcts are small (<15 mm in diameter) noncortical infarcts caused by occlusion of a single penetrating branch of a large cerebral artery.

Etiology

- Microatheroma (commonest cause).
- Lipohyalinosis.
- Small emboli.

Risk Factors

- Hypertension
- Diabetes mellitus
- Smoking
- Hyperhomocysteinemia
- Genetic factors.

Clinical Features

- There are 5 important lacunar stroke syndromes:
  1. Pure motor hemiparesis
  2. Pure sensory stroke
  3. Ataxic hemiparesis
  4. Sensorimotor stroke
  5. Dysarthria-clumsy hand syndrome.

Pure Motor Hemiparesis

- This is the most frequent lacunar stroke syndrome. It is characterized by hemiparesis without any cortical signs (aphasia, agnosia, apraxia, etc.) or sensory deficit. Sometimes weakness may affect only the arm or leg.
- The site of lesion is posterior limb of internal capsule (carries corticospinal and corticobulbar tracts) or basis pontis.

Pure Sensory Stroke

- Pure sensory stroke is defined as numbness of one side of the body in the absence of motor deficit or cortical signs.
- The site of lesion is thalamus.

Sensorimotor Stroke

- This is characterized by both weakness and numbness on one side of the body in the absence of cortical signs.
- The site of lesion is posterolateral thalamus and posterior limb of the internal capsule.

Dysarthria-clumsy Hand Syndrome

- This is the least common of all lacunar syndromes.
- This is characterized by facial weakness, dysarthria, dysphagia, and weakness and clumsiness of one hand. There are no sensory deficits or cortical signs.
- The site of lesion is contralateral pons or internal capsule.

Investigations

- CT scan—less sensitive in picking up lacunar infarcts.

- MRI scan—more sensitive than CT scan.
- CT-angiography or MR-angiography to rule out major artery block.

Treatment

- *Thrombolytic therapy*: Intravenous recombinant tissue-type plasminogen activator or rt-PA if the patient presents within 3 hours.
- Aspirin (75–300 mg) daily.
- Treatment of underlying risk factors such as diabetes, hyperlipidemia, etc.

Q. Draw a diagram of circle of Willis and list the common sites of aneurysm formation.

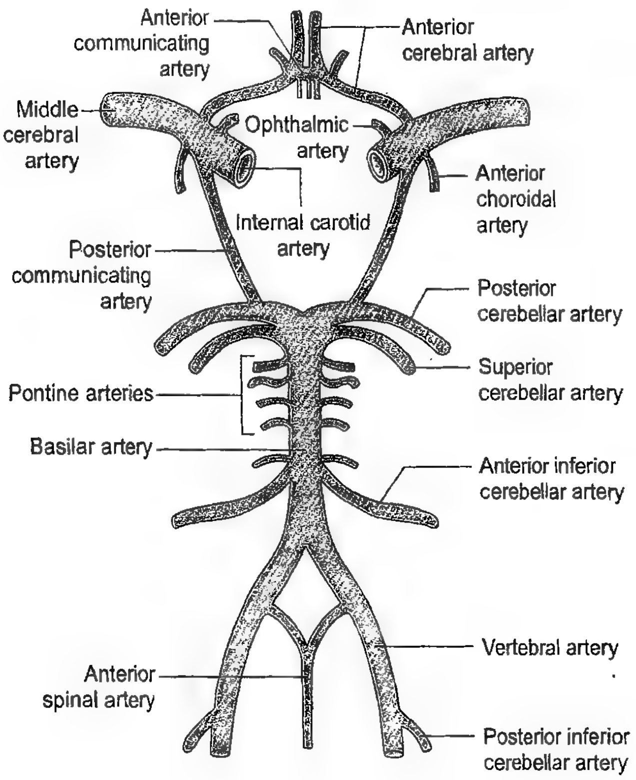

Fig. 5.6: Circle of Willis

- Circle of Willis is formed by the anastomosis between two internal carotid arteries and two vertebral arteries. This extensive anastomosis helps in maintaining the blood supply to brain even when a major feeding vessel gets blocked.
- Aneurysms can occur in the circle of Willis especially at the branching points. Most of the aneurysms occur in the anerior circulation of circle of Willis.

Anterior Circulation Sites

- Junction of the anterior communicating artery with the anterior cerebral artery.
- Junction of the posterior communicating artery with the internal carotid artery
- Bifurcation of the middle cerebral artery.

Posterior Circulation Sites

- Top of the basilar artery.
- Junction of the basilar artery and the superior or anterior inferior cerebellar arteries.
- Junction of the vertebral artery and the posterior inferior cerebellar artery.

Q. Discuss the etiology, clinical features, investigations and management of subarachnoid hemorrhage.

- Subarachnoid hemorrhage (SAH) is bleeding into the subarachnoid space.

Etiology

- Rupture of saccular aneurysms (most common cause)
- Trauma
- Arteriovenous malformations/fistulae
- Vasculitis
- Intracranial arterial dissections
- Amyloid angiopathy
- Bleeding diatheses
- Illicit drug use (cocaine and amphetamines)
- Unknown cause

Risk Factors

- Cigarette smoking
- Hypertension
- Alcohol
- Family history
- Phenylpropanolamine (used in cold remedies, increases the risk of hemorrhagic stroke)
- Estrogen deficiency (this may be the cause of increased risk of SAH in post-menopausal women)
- Anticoagulant use.

Clinical Features

- Symptoms of SAH begin abruptly.
- Main symptom is a sudden, severe headache (thunderclap headache) classically described as the "worst headache of my life." Headache is usally diffuse. Some patients have warning headaches preceding major hemorrhage for many days.
- Headache may be associated with brief loss of consciousness, seizure, nausea, and vomiting.
- Examination reveals variable level of consciousness, neck stiffness and Kernig's sign. Subhyaloid hemorrhage is seen on fundoscopy occasionally.

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Investigations

CT Scan Head

- Plain CT head is the cornerstone of SAH diagnosis. Clot is demonstrated in the subarachnoid space in most cases if the scan is done within 24 hours of the bleed. There may be intracerebral and intraventricular extension of blood in some cases. The sensitivity of head CT for detecting SAH is highest in the first 12 hours after SAH (nearly 100 percent) and then decreases over time. Minor bleed may not be picked up on CT scan.

Lumbar Puncture

- Lumbar puncture should be done in all cases if there is a strong suspicion of SAH despite a normal head CT. The classic findings are an elevated opening pressure and a uniformely blood stained CSF.
- Blood can be present in CSF due to traumatic tap and it should be differentiated from SAH. Clearing of blood (a declining RBC count with successive collection tubes) suggests traumatic tap. If the last tube is normal, it reliably excludes SAH.
- Xanthochromia (pink or yellow tint) represents hemoglobin degradation products. Xanthochromia in CSF is highly suggestive of SAH because blood has to be present in CSF for few hours for it to occur.

Angiogram

- It helps to identify the nature and location of lesion that causes SAH such as AV malformations and aneurysms. It also gives necessary details for neurosurgeon to ligate the aneurysm.

CT or MR Angiography

- This is a noinvasive way of imaging crebrovascular anatomy. Hence, it has replaced conventional angiogram as the initial diagnostic test of choice.

Treatment

General Measures

- Admit the patient in intensive care unit
- Bed rest, stool softeners, adequate analgesia to diminish hemodynamic fluctuations
- Deep venous thrombosis (DVT) prophylaxis with pneumatic compression stockings.
- Discontinue all anticoagulants and antiplatelet agents if the patient is taking any. Anticoagulant effect should be reversed immediately with vitamin K and fresh frozen plasma.

Reduction of Intracranial Pressure (ICP)

- Head end elevation
- Mannitol 20%, 100 ml IV every 6th to 8th hourly
- Loop diuretics (e.g. furosemide) also can decrease ICP.
- Use of intravenous steroids (e.g. dexamethasone) for decreasing ICP is controversial.

Reduction of Blood Pressure

- If BP is high, it should be lowered by using labetalol infusion. Vasodilators such as nitroprusside or nitroglycerin should be avoided because they increase cerebral blood volume and therefore increase intracranial pressure.

Prevention of Vasospasm

- Nimodipine 60 mg every four hours by mouth or nasogastric tube.

Seizure Prophylaxis

- Antiepileptic drugs (phenytoin, sodium valproate) should be given to prevent seizures. Long term seizure prophylaxis is not required.

Treatment of Aneurysms and AV Malformations

- Placement of a clip across the neck of the aneurysm remains the treatment of choice for most aneurysms. Endovascular techniques with coil placement are becoming popular for obliteration of aneurysms and AV malformations.

Complications

- Rebleeding is the most dreaded complication of SAH. It usually occurs within the first 24 hours.
- Vasospasm (presence of blood in the subarachnoid space causes smooth muscle contraction and vasospasm. Vasospasm can lead to brain ischemia and infarction).
- Hydrocephalus can occur due to obstruction of free CSF flow by the presence of blood in the subarachnoid space.

Q. Discuss the etiology, clinical features, investigations and management of intracerebral hemorrhage.

- Intracerebral hemorrhage refers to bleeding within the brain parenchyma. This is the most common type of intracranial hemorrhage. Symptoms are due to mass effect of bleeding and associated edema.

Epidemiology

- Intracerebral hemorrhage is common in old age. However it can also occur in young people due to rupure of arteriovenous malformation. It is more common in men. Incidence is high in Asians and African Americans.

Etiology

- Head injury
- AV malformation or aneurysm rupture
- Cavernous angioma
- Capillary telangiectasias
- Hypertension (usually causes hemorrhage into the putamen)
- Large infarct (bleeding can occur into the infarct)
- Cortical venous sinus thrombosis (can cause hemorrhagic infarct)
- Cerebral amyloid angiopathy (occurs in elderly)
- Drugs (cocaine, amphetamine, phenylpropranolamine)
- Anticoagulant therapy
- Brain tumor (hemorrhage can occur into a tumor)
- Vasculitis (polyarteritis nodosa or SLE)
- Sepsis (may cause small petechial hemorrhages in the brain)
- Moyamoya disease (it is an occlusive arterial disease which can occasionally cause intracerebral hemorrhage)
- Coagulopathy.

Risk Factors

- Alcohol consumption
- Aging
- Diabetes mellitus

Clinical Features

- Patients present with sudden onset of headache, focal neurologic deficits, and impaired consciousness. Headache, vomiting, and impaired consciousness occur due to increased intracranial pressure. Some patients may present in coma.
- Intracerebral hemorrhages especially hypertensive hemorrhages occur when the patient is active.
- Seizures occur in some patients and are more common in lobar hemorrhages involving cerebral cortex (due to irritation of the cortex).
- Patients may complain of a stiff neck and have meningismus on physical examination, if there is extension to ventricles and subarachnoid space.
- Neurologic symptoms and signs vary depending upon the location of the hemorrhage and usually increase gradually over minutes or a few hours.
- Putaminal hemorrhage causes hemiplegia, hemisensory loss, homonymous hemianopia, gaze palsy, stupor, and coma.
- Cerebellar hemorrhage causes an inability to walk due to imbalance, vomiting, headache (which is usually occipital), neck stiffness, gaze palsy, and facial weakness. There is no hemiparesis. Patient may slip into coma due to brainstem compression.
- Thalamic hemorrhage produces hemiparesis, hemisensory loss, and occasionally transient homonymous hemianopsia.
- Lobar hemorrhage produces unilateral hemiparesis and hemisensory deficits. Speech impairement can occur if dominant hemisphere is involved. Occipital hemorrhages present with contralateral homonymous hemianopia.
- Pontine hemorrhage produces deep coma due to disruption of the reticular activating system. There is total paralysis. Pupils are pinpoint and react to a strong light source.

Differential Diagnosis

- Ischemic stroke
- Seizure
- Migraine
- Subarachnoid hemorrhage
- Metabolic encephalopathy

Investigations

CT Scan Head

- Plain CT head is the investigation of choice to diagnose intracerebral hemorrhage. CT can provide information about the size and location of the hematoma, extension into the ventricular system, the presence of surrounding edema, and shifts in brain contents (herniation). Hyperacute blood will appear hyperdense (white appearance). Over weeks, it will appear isodense and later becomes hypodense.

MRI Head

- MRI and CT are equivalent for the detection of acute ICH, but MRI is more accurate for the detection of chronic ICH.

Other Tests

- Routine tests such as blood sugar, urea, creatinine, electrolytes, lipid profile and complete hemogram should be obtained.

Management

- Admit the patient in ICU for continuous neurological and hemodynamic monitoring.
- All anticoagulant and antiplatelet drugs should be discontinued for at least one to two weeks after the onset of hemorrhage and any anticoagulant effect should be reversed immediately with appropriate agents.
- *Blood pressure control*: BP is often elevated in patients with ICH and in hypertensive hemorrhage. BP should be controlled with intravenous nitroprusside, nicardipine, or labetalol. The goal is to maintain the systolic pressure

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between 140 and 160 mm Hg. BP less than this may compromise cerebral perfusion.

- *Surgery*: Surgical evacuation is indicated for all cerebellar hemorrhages greater than 3 cm in diameter since there is a high risk of brainstem compression and obstructive hydrocephalus. Surgical evacuation is also indicated in lobar hematoma if there is gradual deterioration of neurological deficits.
- *Managing raised ICP*:
  - Hyperventilation
  - Mannitol
  - Inj frusemide 20 mg IV Q 6th hourly
  - Elevation of head of bed.
- *Prevention of seizures*: Inj phenytoin 15 mg/kg body weight loading dose given as IV infusion over 30 mins, then 100 mg every 8th hourly
- *Hemostatic therapy*: If the patient presents within 3 hours of onset, treatment with activated recombinant factor VIIa (rFVIIa) may stop the ongoing hemorrhage and hematoma enlargement. Factor VIIa promotes hemostasis at sites of vascular injury.
- *General measures*: Take care of ABCs (airway, breathing circulations), DVT prophylaxis, nutrition (RT feeds, IV fluids).

Q. Causes of hemiplegia in an elderly male.

Hemiplegia is paralysis of one side of the body.

Table 5.16 Causes of hemiplegia

Acute onset	Subacute onset
• Thrombosis • Embolism – *Artery to artery embolus (from carotid, aortic dissection),* – *Cardioembolic (atrial fibrillation, mural thrombus, myocardial infarction, dilated cardiomyopathy, valvular lesions, infective endocarditis)* • Intracerebral hemorrhage • Subarrachnoid hemorrhage with intracerebral extension • Trauma	• Cerebral metastases • Subdural hematoma • Granulomas (tubercular, fungal) • Brain abscess • Cortical vein thrombosis **Chronic** • Slowly growing neoplasms

Q. Causes of stroke in young.

- Stroke in young refers to stroke occurring in individuals of less than 45 years.
- The underlying cause of stroke in young should be identified and treated. Treatment is same as those in elderly.

Table 5.17 Causes of stroke in young

Hypercoagulable disorders • Protein C deficiency • Protein S deficiency • Antithrombin III deficiency • Antiphospholipid antibody syndrome (APLA) • Factor V Leiden mutation • Systemic malignancy • Sickle cell anemia • β-thalassemia • Polycythemia vera • Homocysteinemia • Oral contraceptives • Dysproteinemias • Nephrotic syndrome • Dehydration	**Drug abuse** • Cocaine, amphetamine **Cardiac disorders (cardio-embolic)** • Atrial fibrillation • Atrial myxoma • Intracardiac tumor • Infective endocarditis • Libman-Sacks endocarditis • Myocardial infarction (mural thrombus) • Dilated cardiomyopathy • Paradoxical embolism (atrial septal defect, patent foramen ovale) • Valvular heart diseases (MS, MR, AS, AR)
Connective tissue diseases • Systemic vasculitis (PAN, Wegner's, Takayasu's, giant cell arteritis) • Systemic lupus erythematosus • Inflammatory bowel disease **Infections** • Syphilis • Meningitis • Tuberculosis • HIV	**CNS lesions** • AV malformations • Aneurysms • Neoplasms **Bleeding diathesis** • Thrombocytopenia • Hemophilia • Liver failure

Q. Transient ischemic attack (TIA)

- Transient ischemic attack (TIA) is focal brain ischemia that causes sudden, transient neurologic deficits and is not accompanied by permanent brain infarction.
- The symptoms of TIA usually last less than one hour. Deficits that resolve spontaneously between 1 and 24 h are often accompanied by infarction and are thus no longer considered TIAs.
- TIAs increase the risk of subsequent stroke.

Causes of TIA

Risk factors for TIA are the same as those for ischemic stroke. Modifiable risk factors include the following:

- Alcoholism
- Hypertension
- Cigarette smoking
- Dyslipidemia
- Diabetes
- Obesity
- Lack of physical activity
- High-risk diet (e.g. high in saturated fats, trans fats, and calories)

- Heart disorders (particularly disorders that predispose to emboli, such as acute MI, infective endocarditis, and atrial fibrillation)
- Drugs (e.g. cocaine, amphetamines)
- Hypercoagulable states
- Vasculitis

Unmodifiable risk factors include the following:
- Prior stroke
- Old age
- Family history of stroke
- Male sex

Clinical Features

- Neurologic deficits are similar to those of strokes. Symptoms and signs depend on the blood vessel and the brain area that is affected.
- Features of anterior circulation TIA (carotid system) include amaurosis fugax (transient monocular blindness due to ophthalmic artery involvement), aphasia, hemiparesis, hemisensory loss, and hemianopic visual loss.
- Features of posterior circulation TIA (vertebrobasilar system) include diplopia, vertigo, vomiting, dysarthria, ataxia, transient global amnesia, and loss of consciousness.

Differential Diagnosis

- TIAs must be distinguished from other transient episodes such as following:
  - Focal epilepsy
  - Hypoglycemia
  - Migraine aura
  - Cardiac arrhythmias
  - Syncopal attack

Investigations

- MRI or CT head to rule out any intracranial pathology.
- Carotid and vertebral artery Doppler to rule out stenosis.
- MR angiography
- ECG and echocardiogram to rule out cardiac problems.
- 24-hour ECG monitoring (Holter monitoring) to rule out transient arrhythmias
- Other routine tests (blood sugar, lipid profile, CBC, ESR, electrolytes, urea, creatinine)

Treatment

Antiplatelet Agents

- Aspirin (75 mg daily) reduces the risk of stroke.
- Clopidogrel, dipyridamole and ticlopidine are also effective.
- Combined aspirin 75 mg daily and dipyridamole 200 mg twice daily is better than each given alone.

Anticoagulants

- Heparin and warfarin should be given in embolic TIA such as atrial fibrillation.

Surgical Approaches

- *Internal carotid endarterectomy* is recommended if internal carotid artery stenosis greater than 70%.
- Percutaneous transluminal angioplasty (stenting) is an alternative procedure.

Treatment of Risk Factors

- Diabetes, hypertension, dyslipidemia, etc. should be treated. Smoking should be stopped.

Q. Clinical differentiation between hemorrhagic, thrombotic and embolic stroke.

Table 5.18 Differentiation between hemorrhagic, thrombotic and embolic stroke

Feature	Hemorrhagic	Thrombotic	Embolic
• **Time of onset**	During activity	In sleep	Any time
• **Progression**	Over minutes and hours	Over hours	Within seconds
• **Headache**	Present	Usually absent	Usually absent
• **Vomiting**	Present	Absent	Absent
• **Seizures**	Usually present	Unusual	Unusual
• **Early resolution**	Unusual	Variable	Possible
• **Presence of known bleeding disorder or on anticoagulation**	May be present	Absent	Absent
• **Signs of meningeal irritation**	May be present	Absent	Absent
• **Severe hypertension**	Usually present	May or may not be present	May or may not be present
• **Carotid bruit**	Does not support the diagnosis	Supports the diagnosis	Supports the diagnosis
• **Cardiac disease (valvular heart disease, atrial fibrillation, etc.)**	Does not support the diagnosis	Does not support the diagnosis	Highly supportive

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Q. Amaurosis fugax.

- Amaurosis fugax (from the Greek "amaurosis," meaning dark, and the Latin "fugax," meaning fleeting) refers to a transient loss of vision in one or both eyes.
- Patients with amaurosis fugax are at risk of stroke, myocardial infarction and vision loss. Hence the underlying cause should be identified and treated.

Etiology

Causes of transient monoocular visual loss

- Retinal artery emboli (carotid artery disease, cardiac emboli)
- Retinal vein occlusion
- Retinal vasospasm and retinal migraine
- Optic neuropathy
- Papilledema
- Optic nerve compression
- Idiopathic

Causes of transient binocular visual loss

- Migraine
- Seizure
- Vertebrobasilar ischemia
- Hypotension

Investigations

- Ophthalmologic evaluation
- ESR and C-reactive protein to exclude giant cell arteritis (GCA).
- Carotid Doppler
- MR angiogram to rule out carotid artery dissection
- ECG and echocardiogram to rule out cardiac disease
- EEG if seizyres are suspected
- Hypercoagulable testing in patients prior thrombosis, miscarriage, or family history
- Complete blood count to screen for polycythemia vera and essential thrombocythemia.

Management

- Depends on the cause.

Q. Wallenberg's syndrome (lateral medullary syndrome).

- Wallenberg's syndrome (lateral medullary syndrome) is due to lateral medullary infarction. It can happen due to occlusion of any of five vessels—vertebral, posterior inferior cerebellar, superior, middle, or inferior lateral medullary arteries.

Signs and Symptoms

On the Side of Lesion

- Pain, numbness, impaired sensation over half the face (due to involvement of the spinal nucleus of 5th nerve and the descending spinal tract of 5th nerve)
- Ataxia of limbs, falling to side of lesion (due to involvement of inferior cerebellar peduncle, cerebellar hemisphere, cerebellar fibers, spinocerebellar tract)
- Nystagmus, diplopia, oscillopsia, vertigo, nausea, vomiting (involvement of vestibular nucleus)
- Horner's syndrome (miosis, ptosis, decreased sweating) (involvement of descending sympathetic tract)
- Dysphagia, hoarseness, paralysis of palate, paralysis of vocal cord, diminished gag reflex (involvement of nucleus ambiguous, ninth and tenth nerves)
- Loss of taste (involvement of nucleus and tractus solitarius)
- Numbness of ipsilateral arm, trunk, or leg (involvement of cuneate and gracile nuclei).

On the Opposite Side of Lesion

- Impaired pain and temperature sensation over half the body, sometimes face (involvement of spinothalamic tract)

Investigations

- ***CT or MRI of the brain***: CT scan can be done within a short time and useful in emergencies. However, significant artifacts can occur due to the bony structures surrounding the brainstem and cerebellum. Brainstem leisons are better identified by MRI scan due to the absence of these artifacts.
- ***Other routine tests***: Complete blood count, blood sugar, renal and liver function tests, lipid profile and serum electrolytes.

Treatment

- Admit the patient to ICU.
- Since the patients have dysphagia and are at high risk of aspiration, pass a Ryle's tube and perform endotracheal intubation. Patient should be fed through Ryle's tube to avoid aspiration untill there is improvement of lower cranial nerve dysfunction.
- *Antiplatelets and statins*: Since infarction is the commonest cause of lateral medulary syndrome, antiplatelets such as aspirin and statins such as atorvastatin should be given lifelong.

Q. Discuss the etiology, clinical features, investigations and management of acute viral encephalitis.

- Encephalitis means inflammation of brain parenchyma, usually due to viral infection.
- If both brain and spinal cord are involved, it is referred to as encephalomyelitis.
- Brain inflammation can be associated with meningitis and is known as meningoencephalitis.

Etiology

- Herpes simplex
- ECHO viruses
- Coxsackie
- Mumps
- Epstein-Barr virus
- Influenza virus
- Japanese encephalitis virus
- West Nile virus
- Rabies
- HIV

- Common viruses causing encephalitis are herpes simplex, ECHO, Coxsackie, mumps and Epstein-Barr viruses. Herpes simplex encephalitis is the most common etiology.
- Most of the time viral etiology cannot be confirmed and diagnosis is based on clinical features.
- Viral encephalitis can occur in epidemic and endemic forms in many places. Examples are Japanese encephalitis in South East Asia, California encephalitis in USA, West Nile encephalitis in Egypt and Sudan, etc.
- Rabies is a variety of sporadic viral encephalitis.

Clinical Features

- Symptoms include fever, headache, and altered mental status, often accompanied by seizures and focal neurologic deficits.
- Symptoms and signs of meningeal irritation (photophobia and neck stiffness) are usually absent in encephalitis but may be present in meningoencephalitis.
- Status epilepticus, particularly convulsive status epilepticus, or coma suggests severe brain inflammation and a poor prognosis
- Specific clinical findings may sometimes suggest the causative virus: parotitis suggests the mumps; flaccid paralysis suggests West Nile virus infection; findings of hydrophobia, aerophobia, and hyperactivity suggest rabies virus; grouped vesicles in a dermatomal pattern suggest varicella-zoster virus.

Differential Diagnosis

- Encephalitis should be differentiated from other causes of altered sensorium which are as follows:
  - Meningitis with cerebral edema
  - Cerebral venous thrombosis
  - Cerebral abscess
  - Acute disseminated encephalomyelitis (ADEM)
  - Cerebral malaria
  - Delirium
  - Septicemia

Investigations

- CT and MRI scan may show areas of cerebral edema, often in the temporal lobes.
- EEG often shows characteristic slow waves.
- CSF shows a raised cell count with predominant lymphocytes. CSF sugar is normal and protein is mildly elevated. PCR for herpes simplex and other viral serology (blood + CSF) is helpful to identify the virus.
- Brain biopsy is occasionally performed especially in case of rabies encephalitis.

Treatment

- If herpes simplex encephalitis is suspected, it should be treated immediately with intravenous acyclovir (10 mg/kg IV Q 8 h). There is no specific treatment for other viral encephalitis.
- Supportive treatment involves anticonvulsants, anti-edema measures, bedsore prevention, attention to nutrition through Ryle's tube, IV hydration, Foley catheterization, etc.
- Prophylactic immunization against Japanese encephalitis is advised for travellers to endemic areas in Asia.

Q. Discuss the etiology, clinical features, investigations and management of brain abscess.

- Brain abscess is a focal collection of pus within the brain parenchyma. It behaves as a space occupying lesion.

Etiology

Bacteria (most common cause)
- Streptococcus
- Bacteroides species
- Staphylococci (after trauma or neurosurgery)
- Listeria

Fungi
- Actinomyces
- Nocardia
- Candida
- Aspergillus
- *Coccidioides immitis*

In HIV infected patients
- Toxoplasmosis
- *Cryptococcus neoformans*

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Pathogenesis

- Bacteria can invade the brain either by direct spread, trauma, neurosurgery or hematogenous spread.
- *Direct spread*—Organisms come from a contiguous site such as otitis media, mastoiditis, sinusitis and dental infections.
- *Trauma*—Bullet wounds to the brain can carry bacteria into the brian. Skull fractures can also expose the brain tissue to infections.
- *Neurosurgery*—Brain abscess can also complicate neurosurgical procedures.
- *Hematogenous spread*—bacteria can reach brain through blood from other sources of infection such as lung abscess, empyema, skin infections, pelvic infection, intra-abdominal infection and bacterial endocarditis. Brain abscesses associated with bacteremia usually result in multiple abscesses.

Clinical Features

- Fever and headache is the most common presentation. Since, abscess is a space occupying lesion, it causes symptoms of raised intracranial pressure such as headache, vomiting, and altered sensorium. Headache is localized to the side of the abscess and severe. Focal signs (e.g. hemiparesis, aphasia, hemianopia) and seizures occur depending on the location of the abscess.
- Third and sixth cranial nerve deficits may develop due to raised intracranial pressure.
- Papilledema is a late manifestation of cerebral edema and usually takes several days to develop.

Differential Diagnosis

- Epidural and subdural empyema
- Septic dural sinus thrombosis
- Mycotic cerebral aneurysms
- Septic cerebral emboli with associated infarction
- Focal necrotizing encephalitis
- Neoplasms
- Pyogenic meningitis.

Investigations

- CT head with contrast or MRI scan shows the ring enhancing abscess.
- Lumbar puncture is better avoided as there is risk of herniation due to rased ICP.
- Aspiration with stereotactic guidance allows the infective organism to be identified.
- Serology: Anti-Toxoplasma IgG antibody in blood and anticysticercal antibodies on CSF specimens, can aid in the diagnosis of *Toxoplasma gondii* or neurocysticercosis.

Management

- Treatment of brain abscess usually requires a combination of antibiotics and surgical drainage.
- Streptococcal and anaerobic infections are treated with intravenous cephalosporins plus metronidazole.
- Staphylococcal infections should be treated with flucloxacillin or vancomycin. Other bacteria are treated appropriately.
- Duration of antibiotic therapy is usally 6–8 weeks.
- Glucocorticoids (dexamethasone) should be used when there is significant brain edema causing mass effect and altered mental status.
- Antiepileptics may be required to prevent seizures.
- Surgical decompression may be necessary if parenteral antibiotics are unsuccessful.

Q. Neurocysticercosis.

Etiology

- Neurocysticercosis is the result of accidental ingestion of eggs of *Taenia solium* (i.e. pork tapeworm), usually due to contamination of food by people with taeniasis. Man is the definitive host and pig is the intermediate host.
- When man ingests eggs, they develop into larval cysts called oncospheres, which invade the intestine and are carried by the blood to various organs including brain. In the brain, they remain as cysts for many years which is called neurocysticercosis.

Clinical Features

- Common presentation is seizures. Other symptoms include headache, vomiting, focal neurological signs, and raised intracranial pressure.
- Symptoms are due to mass effect, an inflammatory response, or obstruction of the foramina and ventricular system of the brain.

Investigations

- *CT scan or MRI scan*: Can identify cysts. MRI is more sensitive than CT scan.
- *Serological studies*: Detection of antigen or antibodies to cysticerci can support the diagnosis of neurocysticercosis.

Treatment

- *Asymptomatic neurocysticercosis* need not be treated as treating them may lead to more inflammation and onset of symptoms.
- *Symptomatic neurocysticercosis* should be treated with albendazole or praziquantel. Dose of albendazole is

15 mg/kg per day (usually 800 mg/day) in two divided doses for 15 days. Corticosteroids are usually recommended (30 to 40 mg prednisolone or 12 to 16 mg dexamethasone daily in divided doses) for patients during antihelminthic therapy. Anticonvulsants are indicated to prevent seizures.

- Neurosurgery to removal of cysts is indicated in case of cysts producing mass effect and cysts present in 4th ventricle producing hydrocephalus.

Q. Discuss the classification, etiology, clinical features, investigations and management of epilepsy.

Or

Q. Discuss the etiology, clinical features, investigations and management of grand mal epilepsy (GTCS—generalized tonic clonic seizures).

- A seizure is a transient disturbance of cerebral function due to an abnormal paroxysmal neuronal discharge in the brain.
- Epilepsy is defined as a neurological condition characterized by recurrent epileptic seizures unprovoked by any immediately identifiable cause. Traditionally, the diagnosis of epilepsy requires the occurrence of at least 2 unprovoked seizures.
- A convulsion is a seizure with tonic or clonic muscle contractions.
- Epilepsy is common and its prevalence is about 4 to 8 percent.

Etiology

- The *etiology* of epilepsy is usually multifactorial. Both hereditary and environmental factors play a role. Following are the common causes of epilepsy.
    - Idiopathic (commonest cause)
    - Birth trauma
    - Cerebral anoxia
    - Developmental abnormalities (e.g. microcephaly, porencephaly)
    - Metabolic abnormalities (e.g. hypocalcaemia, hypoglycemia, hypomagnesemia, hyponatremia, uremia, hepatic encephalopathy, phenylketonuria)
    - Infections (meningitis, tuberculosis, congenital syphilis, parasitic infestations)
    - Toxins (heavy metals like lead; carbon monoxide poisoning)
    - Congenital abnormalities (hydrocephalus)
    - Head injury
    - Neoplasm
    - Cerebrovascular disease
    - Degenerative (Alzheimer's disease)

Pathophysiology of a Seizure

- Seizures develop when the balance between excitatory and inhibitory mechanisms is disturbed at the cellular or the synaptic level. Glutamate is the most common excitatory neurotransmitter and gamma-aminobutyric acid (GABA) is the most common inhibitory neurotransmitter involved. Failure of inhibitory processes is increasingly thought to be the major mechanism leading to status epilepticus.
- Spread of electrical activity between neurons is normally restricted. During a seizure, large groups of neurones are activated repetitively, unrestrictedly and hypersynchronously. Inhibitory synaptic activity between neurones fails. This produces high-voltage spike-and-wave EEG activity, the electrophysiological hallmark of epilepsy.
- A focal (partial) seizure is epileptic activity confined to one area of cortex. Focal seizure can spread and involve all parts of the brain. This is called focal seizure with secondary generalization. Seizure can be generalized from the onset. This is called primary generalized seizure.
- Significant physiologic changes occur if seizures are prolonged especially in generalized tonic clonic siezures. These are tachycardia, hypertension, cardiac arrhythmias, hyperglycemia which result from catecholamine surge. Blood pressure may decrease as the seizure activity continues. Body temperature may increase as a result of the vigorous muscle activity and increased sympathetic drive. Marked acidosis usually occurs and has both respiratory and metabolic component. It should not be treated as acidosis is known to have an anticonvulsant effect and resolves with termination of the seizure. Hypoxia occurs due to breathing getting affected by convulsions and also due to aspiration.
- Neuronal death occurs with prolonged seizures due to abnormal neuronal discharges. Neuronal death probably occurs due to the inability to handle large increases in intracellular calcium brought about by prolonged exposure to excitatory neurotransmitters.

Classification

- There are various classifications of seizures. Following is the latest classification of seizures. In the new classification, the word "focal" is used instead of "partial".

Focal onset seizures
- Simple focal seizures (consciousness preserved)
- Complex focal seizures (consciousness is impaired)
- Focal seizures evolving into secondarily generalised seizure

Generalized onset seizures
- Absence seizures

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- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Primary generalized tonic-clonic seizures
- Atonic seizures

Status epilepticus
- Tonic-clonic status
- Focal status
- Absence status

Clinical Features

Focal Onset Seizures

Simple focal seizures
- Involve a part of the brain and consciousness is not lost.
- Simple focal seizure can be motor, sensory, and psychic or associated with autonomic symptoms.
- A simple motor seizure may consist of jerking of one hand or twitching of one half of the face.
- A simple sensory seizure may consist of subjective paraesthesiae involving a hand or a leg.
- They have an abrupt onset and usually last for a few seconds. EEG may show focal spikes. If the seizure focus is deep seated EEG may be normal.

Complex focal seizures
- These also involve a part of the brain but consciousness is impaired or lost. Most of these seizures arise in the temporal lobe.
- A motionless stare with altered consciousness followed by automatisms is the usual pattern. Automatisms are repetitive, purposeless, complex movements such as picking at clothes, smacking lips or swallowing. EEG usually shows abnormal spikes in the area where the seizures originate.
- Psychic symptoms related to memory known as *deja vu and jamais vu* may be seen in complex focal seizures. Deja vu is a feeling of familiarity in an unfamiliar situation, and jamais vu is a feeling of strangeness in a familiar situation.
- *Todd's paralysis* refers to reversible neurological deficit, which lasts less than 48 hours, following a focal seizure.

Focal seizures evolving into secondarily generalized seizures
- Here the seizures start in a focal area of the brain and then spread to involve the whole brain to become generalized seizure.
- "*Jacksonian march*" refers to orderly progression of focal seizure due to the spread of seizure in the cerebral cortex (e.g. from thumb to fingers to face to leg).
- Patient is conscious initially but later loses consciousness when the seizure becomes generalized.

Generalized Onset Seizures (Non-focal Origin)

Absence seizures
- Absence seizures involve brief, sudden lapses of consciousness. There is no aura or postictal confusion. Absence sizures are more common in children and there is significant inherited predisposition for absence seizures.
- Clinical features are vacant stare that lasts 10 to 15 seconds. There will be sudden stop in motion without falling as if frozen. There may be automatic movements such lip smacking, eyelid flutters, chewing motions, finger rubbing, etc. Afterward there is no memory of the incident. Some people have dozens of episodes daily, which interfere with school or daily activities. A decline in a child's learning ability may be the first sign of this disorder. Teachers may comment about a child's inability to pay attention.
- The classic ictal EEG shows 3-Hz generalized spike-and-slow wave complexes.

Myoclonic seizures
- Myoclonic seizures consist of brief jerking motor movements that last less than 1 second and often cluster within a few minutes. It can involve any part of the body, but is mostly seen in limbs or facial muscles. If the seizures evolve into rhythmic jerking movements, they are classified as clonic seizure. Myoclonus is not always pathological. Physiological myoclonus is seen when a person is falling asleep and during early sleep phases. Non-epileptic myoclonus is also seen in hypoxia, drug toxicity and metabolic disturbances. In myoclonic seizure, EEG shows fast polyspike-and-slow wave complexes.

Clonic seizures
- Clonic seizures consist of rhythmic jerking motor movements. They can be focal or generalized.

Tonic seizures
- These are associated with intense stiffening of the body. There is no convulsive jerking. They occur most often during sleep, usually in children. The cause is usually the Lennox-Gastaut syndrome. Tonic (sustained) contraction of axial muscles may begin abruptly or gradually, then spread to the proximal muscles of the limbs. Tonic seizures usually last 10 to 15 sec.

Generalised tonic-clonic seizures (earlier called grand mal seizures)
- These begin with sudden loss of consciousness.

- All muscles of the arms and legs as well as the chest and back become stiff which is called tonic phase. The patient may begin to appear cyanotic during this tonic phase. A loud cry may occur in the tonic phase as air is forcibly expelled across constricted vocal cords. Incontinence of urine and faeces may occur.
- After approximately one minute, there is synchronous clonic muscle jerking.
- Following the seizure the patient may be unconscious, confused, complain of a headache, bodyache or feeling weak, and changes in the mood may be noticed for 24 hours. Injuries include tongue bite, head wounds, dislocation of shoulders, and compression fractures of vertebrae.
- Serum levels of prolactin and creatine phosphokinase are elevated following a seizure.
- The interictal EEG may show generalised spikes, which may or may not be followed by waves, sharp waves and slow waves.

Atonic seizures

- Sudden loss of postural tone, with falling and loss of consciousness.

Differential Diagnosis

- Syncope (e.g. cardiac arrhythmia, vasovagal syncope, dysautonomia)
- Metabolic conditions (e.g. hypoglycemia, hyponatremia)
- Migraine (e.g. migrainous aura, migraine equivalent)
- Transient ischemic attacks
- Sleep disorders (e.g. cataplexy, narcolepsy, night terror)
- Movement disorders (e.g. paroxysmal dyskinesia, chorea)
- Psychiatric conditions (e.g. conversion, panic attacks, breath-holding spells, malingering)

Investigations

Neuroimaging

- CT or MRI scan should be done to exclude a structural brain lesion which could be the cause of seizures.
- MRI is better than CT to identify lesions such as cortical dysplasias, infarcts, or tumors. However, in an emergency situation CT scan is suitable to exclude a mass lesion, hemorrhage, or large stroke because it can be done faster and also more widely available.
- PET scan (positron emission tomogram) can show the seizure focus as hypermetabolizing area.

Electroencephalography (EEG)

- EEG is an essential study in the evaluation of epileptic seizures. It can help confirm the diagnosis and also differentiate between generalized and partial seizures. However, a normal EEG does not rule out epilepsy. Video-EEG monitoring is very helpful for confirming or classifying the type of seizure or for diagnosing pseudoseizures. Video-EEG records EEG activity and clinical behavior simultaneously, usually for 2 to 7 days. However, it is expensive and time consuming, hence monitoring all patients is impractical. Only those who do not respond to treatment or in whom pseudoseizures are suspected should undergo video-EEG.
- Use of provocation techniques such as sleep deprivation, hyperventilation and intermittent photic stimulation, increase the sensitivity of EEG.

Prolactin Levels

- Serum prolactin concentration may rise and remain elevated for up to 6 hours after an epileptic attack.

Lumbar Puncture

- This is helpful to exclude CNS infections such as meningitis if there are clinical features suggestive of meningitis along with seizures.
- It should be done only after a space occupying brain lesion has been excluded by neuroimaging.

Treatment

During an Attack

- Put the patient in a safe place away from fire and sharp objects.
- Put the patient in lateral position and insert a padded mouth gag.
- Inj lorazepam 4 mg slow IV OR inj diazepam 10 mg slow IV.

Treatment of Underlying Condition

- For example, correcting hypocalcemia or hypoglycemia; removal of a structural lesion such as brain tumor, vascular malformation, or brain abscess.
- If the underlying cause can be corrected fully and there is no risk of further seizure, antiepileptic treatment is not needed. However after the removal of a brain lesion, a scar may form and act as a seizure focus. Hence such lesions require antiepileptic therapy.

Antiepileptic Drug Therapy

- Antiepileptics are indicated in people with 2 or more episodes of seizures. Choice of antiepileptic drug depends on the type of epilepsy which is given in the following table.
- Antiepileptics should be introduced slowly to minimize side effects, and gradually increased to achieve the

therapeutic levels. If seizures continue to occur even after the maximum dose of first drug, then another antiepileptic drug should be added while keeping the patient on first drug. If seizures are controlled with the second drug, first drug can be gradually withdrawn.

- An attempt can be made to discontinue antiepileptic drugs if the patient is seizure free for at least 2 years with a normal EEG. Drugs should be withdrawn gradually over 2 to 3 months.

Table 5.19 Treatment of eplilepsy

Type of epilepsy	First line drugs	Second line drugs
Primary generalized tonic-clonic	Valproic acid Topiramate Lamotrigine	Phenytoin Levetiracetam Carbamazepine Primidone Phenobarbital
Focal onset	Carbamazepine Phenytoin Lamotrigine Valproic acid	Topiramate Levetiracetam Gabapentin Primidone Phenobarbital
Absence	Ethosuximide Valproic acid	Lamotrigine Clonazepam
Tonic, atonic and myoclonic siezures	Valproic acid Lamotrigine Topiramate	

General Measures

- Avoid precipitating factors such as sleep deprivation, physical stress, blinking lights, loud noise, and alcohol intake.
- Advice the patient to avoid swimming, going to heights, fire and moving machinery.
- Avoid an occupation which puts the patient or public at risk such as driving a public transport vehicle.

Surgical Treatment for Epilepsy

- Surgery is an option for patients with refractory epilepsy not responding to medical therapy.
- Surgical procedures include temporal lobectomy or amygdalohippocampectomy in patients with temporal lobe epilepsy, removal of an identified lesion (lesionectomy) in focal seizures.
- Hemispherectomy or multilobar resection is useful for some patients with severe seizures due to hemispheric abnormalities, and corpus callosotomy has been shown to be effective for tonic or atonic seizures.

Vagus Nerve Stimulation (VNS)

- VNS is a new treatment option for patients with medically refractory epilepsy who are not candidates for resective brain surgery.
- It involves repetitive electrical stimulation of left vagus nerve by a subcutaneous generator placed in the infraclavicular region.
- The exact mechanism of action of VNS is unknown, although it is supposed to increase seizure threshold.

Q. Status epilepticus.

- Current definition of status epilepticus is continuous seizures lasting more than 5 minutes or two or more sequential seizures without full recovery of consciousness between seizures. Status epilepticus is an emergency and must be treated immediately.

Types

The term status epilepticus may be used to describe continuing seizure of any type.

- Simple partial
- Complex partial
- Generalized tonic-clonic
- Absence
- Myoclonic.

Causes of Status Epilepticus

- Anticonvulsant withdrawal or noncompliance
- Metabolic disturbances (hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia)
- Drug intoxication or withdrawal
- CNS infection (encephalitis, abscess)
- CNS lesions (tumors, AV malformations)
- Cerebral hypoxia
- Refractory epilepsy
- Head trauma.

Pathophysiology

- Seizures are sustained by excess excitation and reduced inhibition of neurons. Glutamate is the most common excitatory neurotransmitter and gamma-aminobutyric acid (GABA) is the most common inhibitory neurotransmitter involved. Failure of inhibitory processes is increasingly thought to be the major mechanism leading to status epilepticus.
- Significant physiologic changes occur in status epilepticus especially in generalized tonic clonic siezures. These are tachycardia, hypertension, cardiac arrhythmias, hyperglycemia which result from catecholamine surge. Blood pressure may decrease as the seizure activity continues. Body temperature may increase as a result of the vigorous muscle activity and increased sympathetic drive. Marked acidosis usually occurs and has both respiratory and metabolic component. It should not be

treated as acidosis is known to have an anticonvulsant effect and resolves with termination of the seizure. Hypoxia occurs due to breathing getting affected by convulsions and also due to aspiration.
- Neuronal death occurs with prolonged seizures due to abnormal neuronal discharges. Neuronal death probably occurs due to the inability to handle large increases in intracellular calcium brought about by prolonged exposure to excitatory neurotransmitters.

Investigations

- Electrolytes, calcium, magnesium.
- Complete blood count.
- Liver and renal function tests.
- Toxicology screen.
- Anticonvulsant level.
- Arterial blod gas.
- *Other tests as indicated*: Chest X-ray, CT scan or MRI of brain, lumbar puncture, blood cultures.
- EEG also should be obtained.

Treatment

- Take care of ABCs (airway, breathing and circulation). Admit the patient in ICU. Intubate the patient. Insert urinary catheter.
- Do a brief medical and neurologic examination, establish IV line and send samples for investigations.
- Anticonvulsant drugs: Intravenous benzodiazepines are the drugs of choice to terminate a seizure attack (examples; lorazepam or diazepam). Further seizures should be prevented by loading the patient with phenytoin. See the following algorithm.

Inj lorazepam 4 mg slow IV or Inj diazepam 10 mg slow IV
↓ If seizures continue
Inj phenytoin 20 mg/kg IV at 50 mg/min
↓ Seizures continuing
Inj phenytoin (give additional 5–10 mg/kg slow IV)
↓ Seizures continuing
Inj phenobarbitone 20 mg/kg IV at 50–75 mg/kg wt
↓ Seizures continuing
Inj phenobarbitone (give additional 5–10 mg/kg slow IV)
↓ Seizures continuing
Anesthesia with midazolam or propofol

Complications

- Rhabdomyolysis
- Lactic acidosis
- Aspiration pneumonia
- Neurogenic pulmonary edema
- Respiratory failure
- Cardiac injury (due to massive release of catecholamines)
- Neuronal death (due to repetitive firing)

Q. Sodium valproate.

- Sodium valproate (valproic acid) is a broad-spectrum antiepileptic drug used alone or in combination for the treatment of generalized and focal seizures.

Pharmacokinetics

- Valproate is tightly protein-bound. It is metabolized in the liver by several processes involving oxidation and conjugation.

Mechanism of Action

- It acts by multiple mechanisms.
- Valproate suppreses high frequency, repetitive neuronal firing by blocking voltage-dependent sodium channels. Valproate increases brain gamma-aminobutyric acid (GABA) concentrations which is an inhibitory neurotransmitter. Valproate also acts against T-type calcium currents.

Dosage and Route of Administration

- The initial dose is 15 mg/kg per day in three divided doses; it may be increased by 5 to 10 mg/kg per day every week as needed. A serum level should be checked one to two weeks after the initial dose; therapeutic concentrations are usually in the 50 to 150 mcg/ml range.
- Valproate can be given by both oral and intravenous (IV) routes. IV administration should be slow over 60 minutes.

Side Effects

- Weight gain and obesity, nausea, vomiting, hair loss, easy bruising, and tremor.
- Valproate can also cause thrombocytopenia and subclinical hypothyroidism.
- Most important side effect is liver failure. Hence, LFTs should be monitored every 6 months to 1 year.
- A syndrome of reversible parkinsonism and cognitive decline has been described with valproate use. The parkinsonism does not respond to levodopa therapy, but usually reverses within a few weeks to months after valproate is discontinued.

Q. Levetiracetam.

- Levetiracetam is an antiepileptic drug. It is a pyrrolidone derivative.

Mechanism of Action

- Exact antiepileptic mechanism is unknown. It may inhibit voltage-depedent N-type calcium channels; may bind to synaptic proteins that modulate neurotransmitter release; may facilitate GABA-ergic inhibitory transmission.

Pharmacokinetics

- Levetiracetam is available as oral and IV preparation. After oral administration, absorption is rapid, with peak plasma concentrations occurring in about an hour. It has got 100% oral bioavailability. It is metabolized in the liver by enzymatic hydrolysis. Plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. It is excreted through renal clearance. Hence dose has to be reduced in renal failure. No dose adjustment is needed for patients with hepatic impairment.

Indications

- Generalized tonic clonic seizures
- Focal onset seizures
- Myoclonic seizures

Side Effects

- Suicidal behavior and ideation
- Somnolence, fatigue
- Serious Dermatological Reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but can occur.
- Coordination difficulties
- Hematologic abnormalities such as agranulocytosis
- Pregnancy category C

Q. Extradural haematoma.

- Extradural hematoma is accumulation of blood between the skull and the dura (extra or epidural).
- It usually occurs after head injury due to rupture of the middle meningeal artery, its branches or the accompanying veins.

Clinical Features

- Most patients are unconscious when first seen.
- A "lucid interval" of minutes to hours before coma supervenes can be seen in epidural hemorrhage, but uncommon.
- The enlarging hematoma compresses and shifts the underlying brain. The rising intracranial pressure results in transtentorial herniation of the medial temporal lobe (uncal herniation) with consequent pressure on the brainstem, the third nerve and the posterior cerebral artery.
- Pressure on braistem leads to unconsciousness. If not relieved promptly, pressure on the brainstem may lead to irreversible brainstem hemorrhage, resulting in respiratory and cardiac arrest.

Diagnosis

- Immediate CT scan should be done if extradural hematoma is suspected. Extradural hematoma is seen as a biconvex high-attenuating lesion between the skull and the brain, with shift of the midline to opposite side.

Treatment

- Evacuation of the hematoma through burr holes.

Q. Subdural hematoma.

- This is accumulation of blood beneath the dura. It happens due to tear of bridging veins running between the cortical surface and the dural venous sinuses. The hematoma is usually associated with contusion/laceration of the brain.
- It can be acute (manifests within 3 days of injury), subacute (manifests within three weeks), and chronic (present after three weeks). The earlier, a hematoma becomes symptomatic the more serious it is.

Clinical Features

- Clinical features are due to expanding hematoma and associated brain injury and edema.
- Majority of these patients are unconscious from the time of injury, and manifest focal symptoms and signs of brain injury or compression.
- Raising intracranial pressure may result in headache and tentorial herniation.

Diagnosis

- The diagnosis can be confirmed by CT scan

Treatment

- Antiepileptics.
- Antiedema measures (mannitol, diuretics, head end elevation).
- Surgical evacuation is indicated if the hematoma is big (25–30 ml), causing mass effect and the patient fails to improve on conservative management.

Q. What are the movement disorders? Enumerate movement disorders.

Q. Classify involuntary movements.

Q. Mention the CNS disorders characterized by involuntary movements.

- Movement disorders are characterized by either reduced (hypokinetic) or excessive (hyperkinetic) activity. Movement disorders are mainly due to diseases of basal ganglia.

Hypokinesia
- Parkinsonism
- Wilson's disease
- Huntington's disease

Hyperkinesia
- Tremor
- Dystonia
- Chorea
- Athetosis
- Ballismus
- Tics
- Myoclonus
- Serotypy
- Akathisia
- Restless legs
- Paroxysmal dyskinesias
- Myokymia

Q. Classify parkinsonism.

- Parkinsonism is a bradykinetic movement disorder characterized by akinesia, rigidity and gait disturbance.

Classification

Primary (idiopathic) parkinsonism
- Parkinson's disease

Secondary (acquired) parkinsonism
- *Infections*: Postencephalitic, SSPE.
- *Drugs*: Phenothiazines, metoclopramide, reserpine, alpha-methyl-dopa.
- *Toxins*: MPTP, manganese, CO, Hg, methanol.
- *Vascular*: Multi-infarct.
- *Trauma*: Punch-drunk syndrome
- *Others*: Hypothyroidism, paraneoplastic

Parkinsonism plus (multisystem degenerations)
- Progressive supranuclear palsy (PSP)
- Multiple system atrophy
- Striatonigral degeneration
- Olivopontocerebellar atrophy
- Shy-Drager syndrome (SDS)

Heredodegenerative parkinsonism
- Autosomal dominant Lewy body disease
- Wilson's disease
- Huntington's disease

Q. Describe the etiology, clinical features, diagnosis and management of Parkinson disease (idiopathic parkinsonism; paralysis agitans).

- Parkinson disease is an idiopathic, slowly progressive, degenerative disorder characterized by resting tremor, stiffness (rigidity), slow and decreased movement (bradykinesia).
- James Parkinson, a physician based in London, first described this condition. He called it as *The Shaking Palsy*.

Epidemiology

- Parkinson's disease (PD) is seen worldwide with a prevalence of 150/100 000.
- Its peak age of onset is in the 60s. Rarely, PD begins during childhood or adolescence (juvenile parkinsonism). Onset between ages 21 and 40 yr is sometimes called early-onset PD. Genetic causes are more likely in juvenile and early-onset PD.
- It affects both sexes.
- It less prevalent in tobacco smokers than nonsmokers.

Etiology

- The exact etiology of Parkinson's diseases is unknown. Some factors possibly involved are:
  - *MPTP*: Minute doses of methylphenyltetrahydropyridine (MPTP) a toxic product of heroin can cause severe parkinsonism. MPTP-like herbicides have been implicated in the causation of PD.
  - *Genetic factors*: There is clustering of early-onset Parkinson's disease in some families. Mutations in the parkin gene on chromosome 6 have been found in families with autosomal recessive cases of PD and some young apparently sporadic cases.

Pathology

- The main pathology in Parkinson's disease is depletion of the dopaminergic neurons of the substantia nigra and degeneration of the nigrostriatal tract.
- The degenerating neurons contain Lewy bodies and neurofibrillary tangles. Lewy body is a highly sensitive marker for PD.
- All these changes result in reduction of striatal dopamine, which is the main biochemical abnormality in PD. Normally an equilibrium exists between acetylcholine and dopamine. With dopamine deficiency, there is acetylcholine hyperactivity which can account for some clinical features such as tremors and rigidity.
- Other neurotransmitters such as norepinephrine, serotonin, somatostatin, substance P, and the enkephalins are also decreased in Parkinson's disease. Depression may be related to reduction of noradrenaline and serotonin in the brain.

Clinical Fetaures

- The symptoms start insidiously and tend to be unilateral or asymmetrical at the onset. The rate of progression is very variable, with a benign form running over several decades. Usually the course is over 10–15 years, with death resulting from bronchopneumonia.
- The initial manifestations may be tremor, slowness, stiffness or clumsiness of an arm or, less commonly, of a leg.
- The classical triad of tremor, rigidity and akinesia develop slowly, over months or several years. Limbs and joints feel stiff due to rigidity.
- Fine movements become difficult due to tremors. Writing becomes small (micrographia) and spidery due to tremors and hypokinesia.

Tremor

- The tremor has a frequency of 4–6 Hz, is present mainly at rest (resting tremor) and is suppressed on voluntary movement. Distal muscles are affected more than the proximal, and the rhythmic tremor at the wrists and fingers resembles "pill-rolling" movement. It disappears during sleep and is aggravated by emotional excitement. This tremor may also be seen in the legs or lower jaw.

Rigidity

- Rigidity is present over the entire range of movement (lead-pipe rigidity) and is present equally in both agonist and antagonistic muscles groups. It is seen mainly in the limbs but can also be present in the neck and axial muscles. When rigidity is associated with tremor, smooth 'leadpipe' rigidity is broken up into a jerky resistance to passive movement—known as cogwheel rigidity.

Akinesia

- There is lack (akinesia) or paucity (bradykinesia) of movement. There is difficulty initiating movement. Motor acts like dressing, feeding and walking show a marked slowing. Rapid fine finger movements, such as piano-playing, become indistinct, slow and tremulous. Facial immobility gives a mask-like appearance. Blinking rate is reduced, producing a stare.

Posture and Gait

- The head and body becomes stooped forwards, often with pronounced kyphosis. The arms become flexed at the elbow and wrists. Flexion also occurs in the joints of the legs. The posture is sometimes called 'simian' to describe the apelike forward flexion, immobility and lack of associated hand movements. The gait may be slow or hurried with diminished arm swing.
- Patients may walk rapidly with short steps (festinating gait) as though they are chasing their centre of gravity.
- Sometimes, patient may not be able to initiate walking as if their feet are glued to the floor (called freezing phenomenon).
- Balance deteriorates, and falls are common in later stages of PD.

Speech

- Speech is initially a monotonous and later becomes slurred as a result of akinesia, tremor and rigidity.

Cognitive, Autonomic and Sensory Disturbances

- Patients with PD often become passive and disinterested in daily activities. Slowness of thought process and inattentiveness are often seen. Anxiety and depression is more common. Cognitive disturbances suggestive of frontal lobe dysfunction are common. Dementia may develop in the late stages.
- Autonomic dysfunction such as constipation, increased frequency of micturition, nocturia, and orthostatic hypotension may occur. Skin is greasy and sweating excessive. Subjective sensory dysfunction such as muscle pains, abdominal discomfort, dysaesthesia in feet may be present.

Diagnosis

- Diagnosis is made by clinical features. There is no lab test to confirm the diagnosis. Neuroimaging should be done (CT or MRI) if any other disease is suspected. PD must be differentiated from other diseases shown below which cause slowness and decreased cognitive functions.

Diferential Diagnoses

- Alzheimer's disease
- Multi-infarct dementia
- Sequelae of repeated head injury (e.g. in boxers)
- Hypoxic brain damage
- Hypothyroidism
- Depression.

Treatment

- Treatment of Parkinson's disease can be divided into nonpharmacologic, pharmacologic, and surgical therapy.

Nonpharmacologic Treatment

- Education of both patient and his family about the disease.
- Emotional and psychologic support to the patient.
- Regular physical exercise, physiotherapy and speech therapy may keep the patient more active.
- Good nutritious diet, rich in fiber.

Pharmacologic Treatment

Dopamine agonists

- Dopamine agonist monotherapy is the initial treatment of choice for most of the symptomatic patients. These drugs act directly on postsynaptic dopamine receptors (primarily D_2 type). Compared to levodopa, they are longer acting and thus provide a more uniform action. They can be combined with carbidopa/levodopa and also with anticholinergics and amantadine. Examples of dopamine agonists are pergolide, bromocriptine, pramipexole and ropinirole.

Levodopa/carbidopa combinations

- Carbidopa is combined with levodopa because carbidopa blocks the peripheral decarboxylation of levodopa into dopamine and thus reduces the symptoms of nausea and orthostatic hypotension. Also more levodopa becomes available to cross the blood–brain barrier and act in the brain as dopamine cannot cross the blood–brain barrier. Treatment should be started with low dose and gradually increased.

Levodopa augmentation

- These drugs augment the action of levodopa. Selegiline is a selective and irreversible MAO-B inhibitor. Typically, selegiline is used as initial therapy or is added to alleviate tremor or levodopa-associated wearing-off. Selegiline can cause insomnia. The role of selegiline as neuroprotective therapy is controversial.
- The catechol O-methyltransferase (COMT) inhibitors entacapone and tolcapone also augment the effects of levodopa by blocking the enzymatic degradation of levodopa and dopamine. They decrease the wearing-off symptoms of levodopa.

Anticholinergics and amantadine

- These drugs can be used along with levodopa. Anticholinergics are useful for controlling rest tremor and dystonia. Amantadine has both anticholinergic and dopaminomimetic properties and can reduce drug-induced dyskinesias.

Neuroprotective therapy

- Many agents can slow down the decline of dopaminergic neurons. These agents include śelegeline, coenzyme Q_{10}, vit E, and L-carnitine. Some trials have shown that these drugs delay the progression of parkinsonism.

Surgical therapy

- Several surgical procedures have been studied in advanced Parkinson's disease (PD), including deep brain stimulation (DBS), thalamotomy, and pallidotomy.
- Deep brain stimulation (DBS) causes an effect similar to surgery due to high frequency stimulation of subthalamus and pallidum without producing a lesion.

Q. Write briefly about dystonia.

- Dystonias are sustained involuntary muscle contractions of antagonistic muscle groups in the same body part, leading to abnormal posturing.

Classification of Dystonia

Generalized

- Primary torsion dystonia (PTD) (idiopathic)
- Dopamine-responsive dystonia (DRD)
- Drug-induced dystonia (e.g. metoclopramide, levodopa)
- Following infection (e.g. after viral encephalitis)
- Paroxysmal dystonia (familial)

Focal

- Spasmodic torticollis
- Writer's cramp
- Oromandibular dystonià
- Blepharospasm
- Hemiplegic dystonia (e.g. following stroke)

Treatment

- Treatment depends on the cause.
- Anticholinergics such as trihexyphenidyl are effective for primary dystonia. Tetrabenazine, a monoamine-depleting agent, is also effective in some patients.
- Other effective drugs include baclofen, carbamazepine, valproate, primidone, and lithium.
- Botulinum toxin injections are helpful if drug therapy fails, especially for focal dystonia.
- Neurosurgical treatment, such as stereotactic thalamotomy, or neurostimulation can help in selected cases.

Q. Chorea.

Q. Athetosis.

- Chorea is nonrhythmic, jerky, rapid, involuntary movement. It is not suppressible and involves distal muscles and face commonly.
- Chorea and athetosis result from impaired inhibition of thalamocortical neurons by the basal ganglia. Excess dopaminergic activity may be the mechanism.
- Chorea and athetosis can occur together (called choreoathetosis).

Causes of Chorea

Hereditary

- Benign hereditary chorea
- Lesch-Nyhan syndrome
- Huntington's disease

Acquired

- Physiologic chorea (seen in infants)
- Cerebral palsy
- Sydenham chorea (seen in rheumatic fever)
- After cardiac surgery
- Kernicterus
- Drugs—phenytoin, levodopa, alcohol
- Systemic lupus erythematosus
- Stroke (basal ganglia)

Treatment

- Underlying cause must be treated. Phenothiazines (e.g. haloperidol) and tetrabenazine provide some symptomatic relief.

Athetosis

- Athetosis is a slow form of chorea characterized by twisting, writhing movements (worm like movements).
- It most often accompanies static encephalopathy due to cerebral palsy, kernicterus, prematurity, poststroke hemiplegia, and other causes of early life brain damage.
- Athetosis usually does not respond to pharmacologic therapy.

Q. Sydenham chorea (St Vitus dance).

- Sydenham chorea is one of the major clinical manifestations of acute rheumatic fever and the most common form of acquired chorea in childhood.
- Chorea usually develops 1 to 8 months after the streptococcal infection, whereas carditis and arthritis usually develop within the first month.

Pathology

- The exact pathology of Sydenham chorea is unknown. However, vasculitis involving the basal ganglia, cortex, and cerebellum has been identified in some brains of affected patients.

Clinical Features

- It usually affects children between 5 and 13 years of age.
- The onset usually is insidious but may be sudden.
- The chorea typically begins in the hands, and later involves face and feet also. The movements are rapid, irregular jerks that are continuous while the patient is awake but improve with sleep. The chorea usually is generalized but may be more prominent on one side. Some may have unilateral chorea.

Diagnosis

- The diagnosis is made by clinical features as there is no specific laboratory test.

Treatment

- Sydenham chorea usually improves in 3–4 months.
- Underlying rheumatic fever should be treated with penicillin for at least 10 days followed by antibiotic prophylaxis.
- Chorea can be reduced by many drugs such as valproic acid, phenobarbital, haloperidol, chlorpromazine, and carbamazepine.

Q. Huntington chorea (chronic progressive chorea; hereditary chorea; Huntington's disease).

- Huntington's disease is an autosomal dominant disorder characterized by chorea and progressive cognitive deterioration, usually beginning during middle age.
- Huntington's disease results from a gene mutation causing abnormal repetition of the DNA sequence CAG, which codes for the amino acid glutamine. The resulting gene product, a large protein called huntingtin, accumulates in the neurons and leads to disease via unknown mechanisms.
- Symptoms and signs develop insidiously, starting at about age 35 to 40. The disease is progressive and patients usually die 10–15 years after the onset due to motor dysfunction and dementia. Clinical features are chorea, gait disturbances, emotional disturbances, dementia and postural instability.
- Diagnosis is based on the clinical features, family history and genetic testing.
- Treatment is symptomatic. The psychosis may improve with neuroleptic agents, such as haloperidol, pimozide, fluphenazine, and thioridazine. Anxiolytics and antidepressants may be useful in some patients.

Q. Hemiballismus/Ballismus.

- Hemiballismus is unilateral rapid, nonrhythmic, nonsuppressible, violent flinging movement of the proximal arm and/or leg. It is actually a severe, coarse form of chorea.
- It is usually unilateral (hemiballismus) but rarely it can be bilateral and is called ballismus.

- It is usually caused by infarction or hemorrhage in the contralateral subthalamic nucleus. Other causes are abscess, AV malformation, cerebral trauma, tumor, and multiple sclerosis involving subthalamic nucleus.
- Drugs used in chorea are useful for hemiballismus, but the disorder usually subsides spontaneously within several weeks.
- Prolonged disabling and medically intractable hemiballismus can be treated with contralateral thalamotomy or pallidectomy.

Q. Myoclonus.

- Myoclonus is sudden, brief, jerk-like contractions of a muscle or a group of muscles. These may be single or repetitive jerks.
- Myoclonus can also be a part of epileptic disorders such as myoclonic epilepsy.

Causes

Physiologic

- Sleep
- Infants

Pathologic

- Myoclonic epilepsy
- Wilson's disease
- Encephalitis
- Metabolic encephalopathy
- Post-hypoxic myoclonus
- *Drugs*: Levodopa, tricyclic antidepressants.

Treatment

- Many drugs are helpful to treat myoclonus such as clonazepam, valproate and levetiracetam.

Q. Define tremor. Mention different types of tremors.

- Tremor is defined as a rhythmic and oscillatory movement of a body part. It is caused by alternating or synchronous contractions of antagonistic muscles. It is the most common movement disorder encountered in clinical practice.
- Tremor may be normal (physiologic) or pathologic. Physiologic tremor is in many people during physical or mental stress.
- Tremors can be intermittent or constant, gradual or sudden in onset and vary in severity. The severity of tremor may not be related to the seriousness of the underlying disorder. For example, essential tremor is benign, but symptoms can be disabling.

Pathophysiology

- Various lesions (ischemia, injury, degeneration, metabolic abnormalities) in the brainstem, extrapyramidal system, or cerebellum can cause tremors. Sometimes tremor is a familial condition (e.g. essential tremor).

Types of Tremors

Rest Tremors

- The tremor is evident when the affected body part is supported and at rest and decreases during voluntary activity.
- *Examples*: Parkinson disease, midbrain (rubral) tremor and Wilson's disease.

Action Tremors

- Occur when a body part is moved voluntarily. Action tremors may change in severity as a target is reached. Action tremors include kinetic, intention, and postural tremors.
- *Kinetic tremor* occurs with any form of voluntary movement. Examples are essential tremor, cerebellar, dystonic, and drug-induced tremors
- *Intention tremor* is a subtype of kinetic tremor which worsens as the target is reached. Example: Cerebellar disease.
- *Postural tremor* occurs when a body part is held motionless against the force of gravity (e.g. holding the arms stretched out). *Examples*: Physiologic tremor, essential tremor, primary writing tremor, Parkinson's disease, and Wilson's disease.

Q. Essential tremor.

- Essential tremor is the most common movement disorder characterized by kinetic and/or postural tremors of hands.
- Essential tremor is a benign condition. However, it may interfere with feeding, speaking, writing, and other activities of daily living.

Etiology

- The cause of essential tremor is uncertain but physiologic studies have demonstrated dysfunction of the cerebellar system. It is often inherited as an autosomal dominant trait.

Clinical Features

- Essential tremor occurs at any age but occurs most frequently in the elderly.
- The frequency of the tremor is usually 5–8 Hz, and most often affects the hands and arms. It can also affect the head (titubation), voice, chin, trunk, and legs.

- Tremor develops when the hands adopt a posture, such as holding a glass or a spoon. It is slowly progressive but rarely produces severe disability. Writing is shaky and untidy.
- Anxiety exacerbates the tremor, sometimes dramatically.

Treatment

- Treatment is usually not needed. Patients should be reassured that it is not a serious disease.
- Propranolol and primidone are the most effective and well-studied medications for the treatment of essential tremor.
- Small amounts of alcohol can also reduce the severity of tremor. Sympathomimetics (e.g. salbutamol) worsen the tremor and should be avoided.
- Stereotactic thalamotomy and thalamic stimulation are used in severe cases.

Q. Intention tremor.

- Intention tremor is a subtype of kinetic tremor which worsens as the target is reached. It is due to lesions of cerebellum and its connections. Other causes of intention tremor include Wilson's disease, hepatocerebral degeneration, and mercury poisoning.
- The tremor typically increases in severity as the hand moves closer to its target. Intention tremors are usually coarse due to involvement of proximal muscles. There may be other cerebellar signs such as ataxia, dysmetria, titubation, and dysdiodochokinesia.
- There is no drug available to treat intention tremor. Physical therapy (e.g. weighting the affected limbs, teaching patients to brace the proximal limb during activity) sometimes helps. Patients with severe tremor can be helped by deep brain stimulation of the thalamus.

Q. Eneumerate demyelinating neurological disorders.

- Demyelinating diseases are conditions where there is breakdown of the myelin sheath with relative preservation of axons. This affects the conduction of signals through nerve fibers.
- Examples of demyelinating diseases are as follows.

Idiopathic (Autoimmune)

- Multiple sclerosis
- Transverse myelitis
- Acute inflammatory demyelinating polyneuropathy (AIDP)
- Acute disseminated encephalomyelitis (ADEM).

Viral Infections

- Progressive multifocal leukoencephalopathy
- Subacute sclerosing panencephalitis (SSPE).

Nutritional Disorders

- Suacute combined degeneration (vitamin B_{12} deficiency)
- Demyelination of the corpus callosum (Marchiafava-Bignami disease)
- Central pontine myelinolysis.

Anoxic-ischemic

- Delayed postanoxic cerebral demyelination
- Progressive subcortical ischemic encephalopathy.

Leukodystrophies

- Adrenoleukodystrophy (Schilder's disease)
- Metachromatic leukodystrophy.

Q. Describe the etiology, clinical features, diagnosis and management of multiple sclerosis.

- Multiple sclerosis is an autoimmune disorder characterized by multiple demyelinating lesions in the brain and spinal cord.

Epidemiology

- Multiple sclerosis (MS) is common in Western countries but rare in India and other countries of Asia and Africa.
- It usually affects young people between 15 and 50 years. It has a prolonged course.
- It is about twice as common in women as men.

Etiology

- The exact cause of MS is unknown. It is probably an autoimmune disorder where T cells are activated and destroy the myelin sheath.
- Infection by a latent virus (possibly a human herpesvirus such as Epstein-Barr virus) has been suspected to trigger a secondary autoimmune response leading to MS.
- Genetic factors may play a role as suggested by increased incidence among certain families and presence of human leukocyte antigen (HLA) allotypes (HLA-DR2).
- Environmental factors also play a role in the causation of the disease. The disease is more common in temperate climate (European countries) than tropical climate (Asian countries).

Pathology

- There are multiple areas of demyelination with reactive gliosis (hence called multiple sclerosis) scattered in the white matter of brain, spinal cord and in the optic nerves.

- Demyelination is initiated by inflammation due to the entry of activated T lymphocytes through the blood–brain barrier. There is release of cytokines and attraction of macrophages which destroy the myelin sheath. Histologically, the characteristic lesion is a plaque of inflammatory demyelination occurring most commonly in the periventricular regions of the brain, the optic nerves and the subpial regions of the spinal cord. After an acute attack, gliosis occurs, leaving a shrunken grey scar (sclerosis).
- In the later stages there is destruction of axons also which is responsible for the progressive and persistent disability.

Disease Patterns

- The different patterns of multiple sclerosis are as follows:
  - *Relapsing remitting MS (RRMS)*—this is characterized by relapses with full recovery in between. This is the initial type in most patients. However, most patients will eventually enter a secondary progressive phase.
  - *Secondary progressive MS (SPMS)*—this is characterized by an initial RRMS followed by progression of the disease with minor remissions.
  - *Primary progressive MS (PPMS)*—this is characterized by disease progression from the onset with occasional minor improvements but without any acute attacks.
  - *Progressive relapsing MS (PRMS)*—this is characterized by progressive disease from onset, with acute attacks, with or without full recovery. Progression continues during the periods between disease relapses.

Clinical Features

- The typical patient presents as a young adult with two or more clinically distinct episodes of CNS dysfunction with at least partial resolution.
- The hallmark of MS is symptomatic episodes that occur months or years apart and affect different anatomic locations.

Cranial Nerves

- Optic neuritis is a common presentation and leads to central scotoma. Trigeminal neuralgia can occur.

Motor System

- Motor symptoms are due to lesions of corticospinal tracts and include upper limb weakness, paraparesis or paraplegia. UMN signs such as spasticity, exaggerated deep tendon reflexes, clonus and extensor plantar responses are usually present.

Sensory System

- Sensory symptoms are also very common feature of MS and are due to demyelinating lesions in spinothalamic, posterior column, or dorsal roots. Sensory symptoms are numbness, tingling, pins-and-needles, tightness, coldness, radicular pains, etc.

Cerebellum

- Lesions in cerebellum and its connections can cause cerebellar signs such as ataxia and incordination.

Spinal Cord

- Spinal cord involvement causes bowel, bladder, and sexual dysfunction leading to urgency, urinary incontinence, constipation or fecal incontinence, erectile dysfunction, etc.
- Neuromyelitis optica (Devics disease) is a variant of MS characterized by involvement of only optic nerve and spinal cord. Brain lesions are absent. There are symptoms and signs of motor, sensory and sphincter disturbances.
- Lhermitte's sign also called the barber chair phenomenon, is an electric shock like sensation that runs down the back and into the limbs on flexing the neck. It is caused by involvement of the posterior columns of spinal cord.

Other Features

- Heat sensitivity (Uhthoff's phenomenon) is a well known occurrence in MS; small increases in the body temperature can temporarily worsen current or pre-existing signs and symptoms.

Diagnosis

- Multiple sclerosis should be suspected when multiple areas of the CNS are involved at different times. At least two or more different central white matter lesions should occur at different times (i.e. dissemination in place and time).
- MRI of the brain and cervical cord is the investigation of choice. It shows multiple demyelinating lesions. Lesions are often found in the periventricular area. MRI can identify both old and new lesions in different areas.
- Evoked potential recordings (such as visual evoked response) show prolongation and can detect subclinical involvement of the visual, auditory and somatosensory pathways.
- CSF examination may show lymphocytosis or increased protein concentration. CSF electrophoresis shows oligoclonal bands.

Management

Patient Education

- Patient and family members should be educated about the nature of disease. Patient should be told about the unpredictable course and also emphasize the fact that significant proportion of patients remain neurologically intact for many years.

Acute Attacks

- Acute attacks are treated with corticosteroids. A typical course is methylprednisolone, 1 g intravenously for 3 days followed by oral prednisolone, 60 or 80 mg per day for 1 week, after which it is tapered over next 2 to 3 weeks.
- Plasmapheresis and intravenous immunoglobulins have shown benefit in some trials.
- Relapses are also treated with similar course of steroids.

Preventing Relapses

- Two forms of recombinant beta interferon, interferon β_{1a} and interferon β_{1b}, have been approved for use in relapsing remitting MS patients. Beta interferon therapy reduces the frequency and severity of MS relapses, slows disability progression, reduces the number of new lesions.
- Glatiramer acetate is a polypeptide consisting of basic amino acids. It is thought to inhibit cellular immune reactions to myelin. It reduces the relapse rates.
- Immunosuppressive therapy with cyclophosphamide, azathioprine, methotrexate, cladribine, or mitoxantrone may help arrest the course of progressive multiple sclerosis.
- Treatment with natalizumab, a recombinant monoclonal antibody also reduces relapse rate.

Symptomatic Therapy

- Spasticity—physiotherapy, baclofen, tizanidine, diazepam, injection of botulinum toxin.
- Ataxia—isoniazid, clonazepam.
- Sensory symtoms—carbamazepine, gabapentin, amitriptyline.
- Spastic bladder—anticholinergics like oxybutynin or propantheline.
- Fatigue—amantadine.
- Impotence—sildenafil.
- Depression—imipramine, amitriptyline.

Q. Describe the anatomy of the spinal cord and enumerate the diseases affecting the spinal cord.

Q. Causes of spinal cord compression (compressive myelopathy).

- The spinal cord extends from the lower border of medulla at the foramen magnum till the lower border of L1 vertebra. The tip of the spinal cord is cone shaped and is called conus medullaris. In the lumbosacral region, nerve roots from lower cord segments descend vertically within the spinal canal, forming the cauda equina (so called because of resemblance to horse tail).
- The white matter at the cord's periphery contains ascending and descending tracts of myelinated sensory and motor nerve fibers. The central H-shaped gray matter is composed of cell bodies of neurons and nonmyelinated fibers. The anterior (ventral) horns contain lower motor neurons, which receive impulses from the motor cortex via the descending corticospinal tracts. The axons of the lower motor neurons are the efferent fibers of the spinal

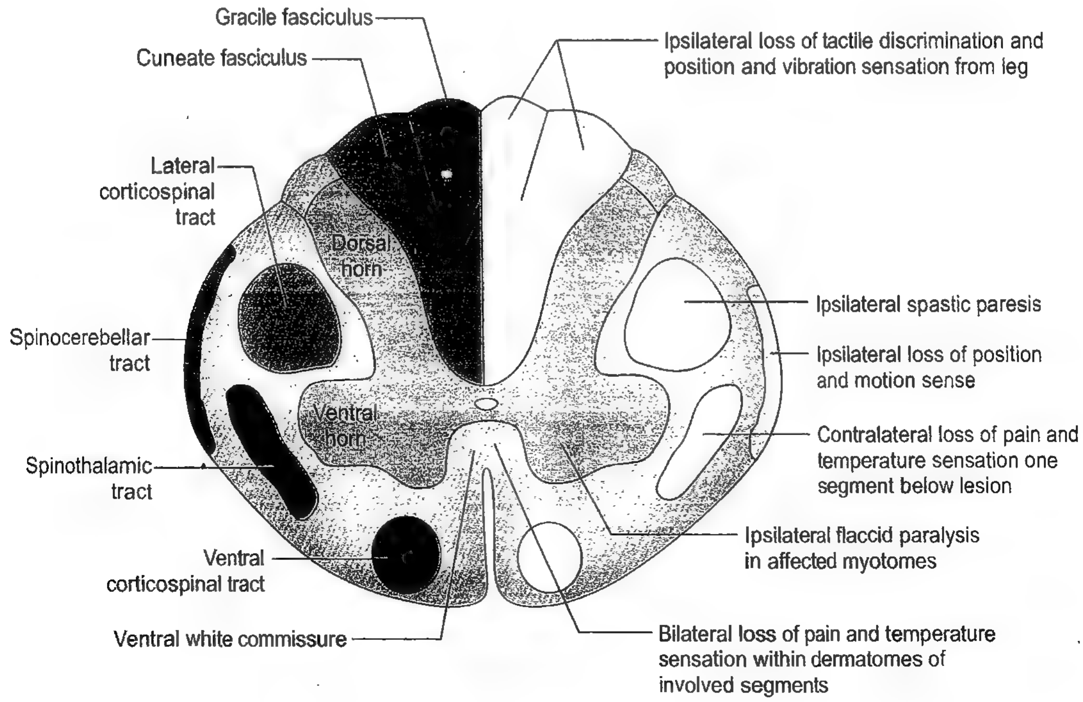

Fig. 5.7: Spinal cord cross section

nerves. The posterior (dorsal) horns contain sensory fibers that originate in cell bodies in the dorsal root ganglia. The gray matter also contains many internuncial neurons that carry motor, sensory, or reflex impulses from dorsal to ventral nerve roots, from one side of the cord to the other, or from one level of the cord to another. The spinothalamic tract transmits pain and temperature sensation contralaterally in the spinal cord; most other tracts transmit information ipsilaterally.

- On each side of the spinal cord, the anterior and dorsal nerve roots combine to form the spinal nerve as it exits from the vertebral column through the neuroforamina. The cord is divided into 31 functional segments corresponding to the attachments of the 31 pairs of spinal nerve roots.
- The blood supply of the spinal cord consists of 1 anterior and 2 posterior spinal arteries. The anterior and posterior spinal arteries arise from the vertebral arteries. The anterior spinal artery supplies the anterior two-thirds of the cord and the posterior spinal arteries supply the posterior one-third.

Diseases affecting the Spinal Cord

- Spinal cord problems are generally reffered to as myelopathies, which are as follows.

Compressive Myelopathy

- ***Extradural:*** TB spine, epidural abscess, epidural tumor, spinal metastases, disc prolapse, spondylosis, lymphomas, extradural AV malformations or hematoma.
- ***Intradural:*** Meningioma, neurofibroma, intradural AV malformations, arachnoiditis.
- ***Intramedullary:*** Syringomyelia, ependymoma, astrocytoma.

Noncompressive Myelopathy

- Transverse myelitis
- Radiation myelopathy
- AIDS myelopathy
- Tropical spastic paraplegia
- Spinal cord infarction
- Multiple sclerosis.

Clinical Features of Spinal Cord Disease

- Spinal cord can be affected both horizontally and vertically to a variable extent. Clinical features depend on how much of the spinal cord is involved horizontally and how much is involved vertically.
- Horizontal lesions of the spinal cord can be grouped into various clinical patterns (syndrome) are given in Fig. 5.8.

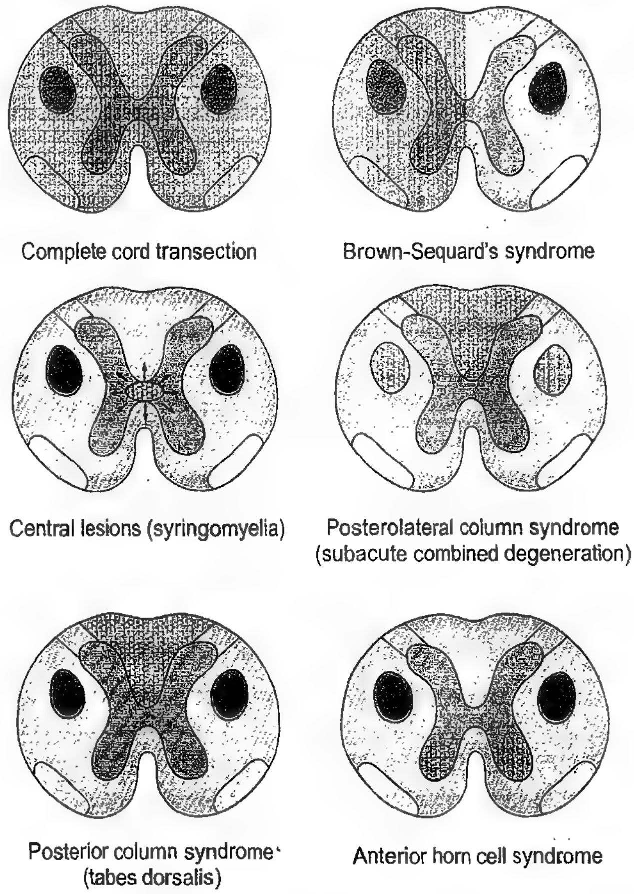

Fig. 5.8: Spinal cord syndromes

Complete Spinal Cord Transection (Transverse Myelopathy)

- With complete cord transection, all ascending tracts from below the level of the lesion and all descending tracts from above the level of the lesion are interrupted. Therefore, all motor and sensory functions below the level of spinal cord damage are disturbed. Transverse myelopathy is a general term for diseases causing complete horizontal damage to spinal cord. Transverse myelitis is a type of transverse myelopathy due to inflammation of the cord.
- *Examples*: Transverse myelitis, traumatic injury.

Hemisection of the Spinal Cord (Brown-Séquard's Syndrome)

- Half of the spinal cord is damaged horizontally. For detailed clinical features see Brown-Séquard's syndrome.
- Examples are traumatic injuries and stab inuries.

Central Cord Lesions

- Disease process starts in the centre of the spinal cord and extends to the peripheral part of spinal cord. Characteristically, the decussating fibers of the spinothalamic tract anterior to the central canal carrying pain and temperature sensation are affected initially. This

results in loss of pain and temperature sensation with the preservation of fine touch and proprioception (dissociation of sensory loss) (see syringomyelia for a detailed description of clinical features)

- *Examples*: Syringomyelia, ependymoma.

Based on the vertical level of lesion, following clinical patterns may be seen

- *At or above C5*: Respiratory paralysis, quadriplegia
- *At C5–C6*: Paralysis of legs, wrists, and hands, weakness of shoulder abduction and elbow flexion, loss of biceps and brachioradialis reflex
- *Between C6 and C7*: Paralysis of legs, wrists, and hands, but shoulder movement and elbow flexion usually possible
- *Between C7 and C8*: Loss of triceps jerk reflex, paralysis of legs and hands
- *At C8 to T1*: Horner syndrome (constricted pupil, ptosis, facial anhidrosis), paralysis of legs
- *Between T1 and conus medullaris*: Paralysis of legs.

Q. Transverse myelitis.

- Transverse myelitis is a neurological disorder caused by inflammation across the entire width of the spinal cord. It may be infective or noninfective. It is a type of non-compressive myelopathy.

Etiology

- *Vascular*: Spinal cord infarction due to spinal artery thrombosis, vasculitis
- *Systemic inflammatory disorders*: SLE, sarcoidosis, Behçet's syndrome and Sjögren's syndrome.
- *Infectious*: Herpes zoster, HSV 1 and 2, EBV, CMV, rabies virus, listeria monocytogenes, lyme disease, and syphilis.
- *Postinfectious*: Epstein-Barr virus (EBV), cytomegalovirus (CMV), mycoplasma, influenza, measles, varicella, rubeola, and mumps.
- *Demyelinating diseases*: Multiple sclerosis and neuromyelitis optica.
- *Idiopathic*: Here, the cause is unknown.

Clinical Features

- The onset of symptoms may be acute or subacute. Thoracic region is most often involved. Common presenting symptoms are pain in the back, limb weakness, sensory involvement, bowel and bladder dysfunction.

Motor Disturbances

- All motor functions are lost below the level of lesion. At the level of leion there are lower motor neuron signs (paresis, atrophy, fasciculations, and areflexia) and below the level of lesion there are UMN type paralysis. Initially, especially with acute lesions, the paralysis is flaccid and areflexic because of spinal shock, but later spastic paraplegia develops.
- There is loss of tendon reflexes in the acute stage due to spinal shock. Subsequently, tendon reflexes become exaggerated and plantar response becomes extensor.
- Abdominal reflexes are absent.

Sensory Disturbances

- All sensory modalities (soft touch, position sense, vibration, temperature, and pain) are impaired below the level of the lesion. A sensory level is present.

Autonomic Disturbances

- Bowel and bladder sphincter dysfunction with incontinence can occur with transverse myelitis. Urgency of micturition is the usual bladder symptom, with urinary retention a later problem. Incontinence of urine is a very late feature. Constipation is the most common bowel symptom. Initially, atonic and, later, spastic rectal and bladder sphincter dysfunction occur with lesions at any spinal level.
- Orthostatic hypotension, loss of weating, trophic skin changes, impaired temperature control, sexual dysfunction (especially impotence) are other features of autonomic dysfunction.

Investigations

- MRI of spinal cord should be done to rule out any alternate pathology (abscess, mass, etc).
- CSF cell count and pressure is usually normal but there is increase in its protein content.

Treatment

- Care of skin, bladder and bowels, and physiotherapy.
- Treatment of choice for idiopathic transverse myelitis is intravenous administration of methylprednisolone.
- If a cause is identified, treatment should be directed towards that.

Q. Brown-Séquard's syndrome.

- The Brown-Séquard's syndrome results from a lesion involving only one side of the spinal cord. It is usually produced by extramedullary lesions.

Etiology

- Road traffic accidents
- Industrial and sports accidents

- Direct injury to the cord with high-velocity missiles or a sharp instrument.
- Infarction of spinal cord
- Intradural tumors.

Clinical Features

- Ipsilateral spastic weakness due to interruption of the descending corticospinal tract below the level of damage. Lower motor neuron signs and sensory deficits at the level of the lesion due to damage to anterior horn cells and motor root.
- Ipsilateral loss of proprioception and vibration below the level of the lesion due to interruption of the ascending fibers in the posterior columns.
- Contralateral loss of pain and temperature sensation due to interruption of the crossed spinothalamic tract. This sensory level is usually one or two segments below the level of the lesion.

Q. Discuss the etiology, clinical features, diagnosis and management of syringomyelia.

Q. Dissociated sensory loss.

- Syringomyelia refers to fluid-filled cavities within the spinal cord. The cavity is called syrinx and is usually found within the cervical or thoracic spinal cord.
- Syringobulbia means a cavity in the brainstem.

Etiology and Pathology

- Syrinxes usually result from lesions that partially obstruct CSF flow which are given in Fig. 5.9.

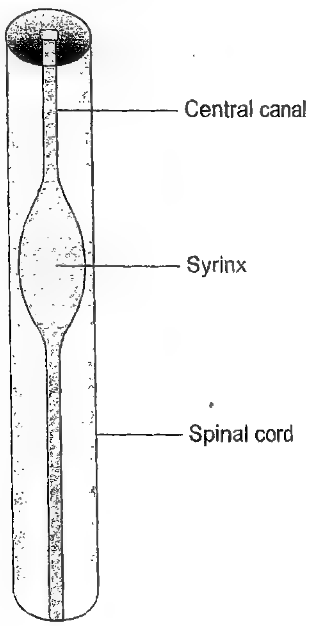

Fig. 5.9: Syringomyelia

- Congenital abnormalities of the craniocervical junction (Chiari type 1 malformation), brain (e.g. encephalocele) or spinal cord (e.g. myelomeningocele).
- Scarring due to spinal cord trauma, myelitis, chronic arachnoiditis due to tuberculosis and other etiologies, necrotic spinal cord tumors.

Clinical Features

- Clinical features depend on the location of the cavity.
- The syrinx is most commonly encountered in the lower cervical region, extending into the central gray matter and anterior commissure. The cyst interrupts the decussating spinothalamic fibers which carry pain and temperature sensation. This results in classic *dissociated sensory loss* where there is loss of pain and temperature sensation with sparing of touch and vibration which are carried by posterior column.
- Symptoms usually start on one side and then the other side gets involved.
- Extension of the cavity to the anterior horns produces segmental weakness, muscle atrophy and areflexia. Lateral extension results in an ipsilateral Horner syndrome (owing to the involvement of the sympathetic system). As the lesion enlarges, corticospinal tract gets involved and spasticity, weakness of the legs, bladder and bowel dysfunction develop.
- Dorsal extension disrupts dorsal column function (ipsilateral position sense and vibratory loss), and with anterolateral extension, the spinothalamic tract is affected, producing loss of pain and temperature below the spinal level of the lesion. Because the sacral fibers are located laterally in the spinothalamic tract, and the disease process starts from the centre of the spinal cord, sacral fibers are spared initially.
- Some patients develop facial numbness and sensory loss from damage to the descending tract of the trigeminal nerve (C2 level or above).
- If the syrinx extends into the brainstem (syringobulbia), there is dysphagia, pharyngeal and palatal weakness, asymmetric weakness and atrophy of the tongue, sensory loss involving primarily pain and temperature sense in the distribution of the trigeminal nerve, and nystagmus.
- Thoracic kyphoscoliosis is usually present due to weakness of paraspinal muscles.

Investigations

- MRI can demonstrate the syrinx cavity.

Treatment

- There is no curative treatment. Treatment depends on the cause.

- If the syrinx cavity is large, decompression of the cavity by syrinx-subarachnoid shunt may produce some benefit.

Q. Describe the etiology, clinical features, differential diagnosis, complications and management of paraplegia.

- Paraplegia refers to paralysis of both lower limbs. Paraperesis refers to partial weakness of both lower limbs.

Etiology

Spinal Cord Diseases

- *See* page no. 354.

Other Causes

- Anterior horn cell disorders
- Cauda equina syndromes
- Peripheral neuropathies
- Guillain-Barré syndrome
- Unpaired anterior cerebral artery ischemia
- Parasagittal meningioma
- Superior sagittal sinus thrombosis

Clinical Features

- Acute spinal cord lesions produce flaccid paraplegia initially due to spinal shock. However, later it becomes spastic. Lesions of peripheral nerves (peripheral neuropathy, GB syndrome) result in flaccid paraplegia.
- Paraplegia in extension is seen when only corticospinal tract is involved, because extrapyramidal system takes over resulting in excess tone of antigravity muscles.
- Paraplegia in flexion is seen when both corticospinal and extrapyramidal sytem is involved, because of increase in tone of flexors.
- Bowel and bladder disturbances and sensory symptoms are common in spinal cord lesions.
- Additional clinical features may be present depending on the underlying cause.

Investigations

- *Plain X-ray of spine*: Can detect degenerative changes of spine (spondylosis), vertebral fractures and any other vertebral disease.
- *MRI spine*: Can visualise in detail the spinal cord and its coverings, spine and disc pathology.
- Appropriate tests to rule out underlying cause.

Complications

- Bedsore
- Limb contracture
- Deep vein thrombosis and pulmonary embolism
- Osteoporosis
- Fecal impaction with intestinal obstruction
- Urinary infection.

Management of Paraplegia

General Measures

- Patient needs both physical and mental support. Good nutritious diet should be provided. Any intercurrent infection is potentially dangerous and should be treated early.

Bladder Care

- Continous indwelling catheter is required initially. However intermittent catheterization is better to prevent infection. Once the patient learns the technique of catheterization he can do it himself. Many develop reflex bladder emptying, helped by abdominal pressure. Free urinary drainage is essential to avoid stasis, subsequent infection and calculi formation.

Bowel Care

- Constipation and fecal impaction are common in paraplegics. These should be avoided by stool softeners, laxatives or regular enemas. Digital evacuation may be necessary if stools are hard and impacted. Reflex rectal emptying develops later and patient can pass stools himself.

Skin Care

- Since a paraplegic patient is bedridden most of the time, there is risk of developing pressure sores. Pressure sores (bedsore) are common over pressure points such as sacrum, iliac crests, greater trochanters, heels and malleoli. They can be prevented by maintaining cleanliness and turning the patient every 2 hours. Ripple mattresses and water beds are very useful to prevent pressure sores. If pressure sores develop, plastic surgical repair should be considered. Pressure palsies (e.g. ulnar nerves and common peroneal) must be avoided.

Lower Limbs

- Paralysed lower limbs are prone to develop contractures and deep vein thrombosis which should be prevented by physiotherapy. Severe spasticity, with flexor or extensor spasms, may be helped by baclofen, diazepam, dantrolene, tizanidine or botulinum toxin injections.

Treatment of the Underlying Cause

- Underlying cause should be identified and treated.

Rehabilitation

- Many patients with paraplegia can become partially or fully independent. Specialist advice from a rehabilitation unit is necessary.

Q. Describe the nerve supply of urinary bladder. Describe various types of bladder dysfunction.

- The bladder is a hollow bag made of a syncytium of smooth muscle with stretch receptors. There is an internal urethral sphincter made of smooth muscle and an external urethral sphincter which is made of striated muscle.

Nerve Supply of Urinary Bladder

Parasympathetic Supply

- S2, S3 and S4 segments through the pelvic nerve.
- Innervate detrussor muscle and internal sphincter.
- Function: Contraction of detrussor muscle and inhibition of internal sphincter.

Sympathetic Supply

- T10 to L2 through the hypogastric plexus.
- Innervate detrussor muscle and internal sphincter.
- Function: Inhibition of detrussor muscle and contraction of internal sphincter.

Somatic Efferent

- S1, S2 and S3 segments through pudendal nerve.
- Innervate external sphincter.
- *Function*: Voluntary contraction of external sphincter.

Afferents

- Arise from bladder wall and internal sphincter and run through the above nerves.
- *Function*: Carry the sensation of bladder distension.

Various Types of Bladder Dysfunction

- Any condition that impairs bladder afferent and efferent nerve supply can cause neurogenic bladder. Causes may involve the CNS (e.g. stroke, spinal cord injury), peripheral nerves (e.g. diabetic peripheral neuropathy, vitamin B_{12} deficiency), or both (e.g. Parkinson's disease, multiple sclerosis, syphilis).
- Mainly there are two broad types of bladder dysfunction due to the above causes.

Flaccid (Hypotonic) Neurogenic Bladder

- It occurs due to cuada equina and sacral segments (S2, S3, S4) damage. It also occurs in the initial stages (stage of spinal shock) of acute cord damage.
- Here, the bladder volume is large, pressure is low, and contractions are absent resulting in urinary retention. Overfolow incontinence can occur when the bladder capacity is exceeded.

Spastic Bladder

- It results from brain damage or spinal cord damage above T12.

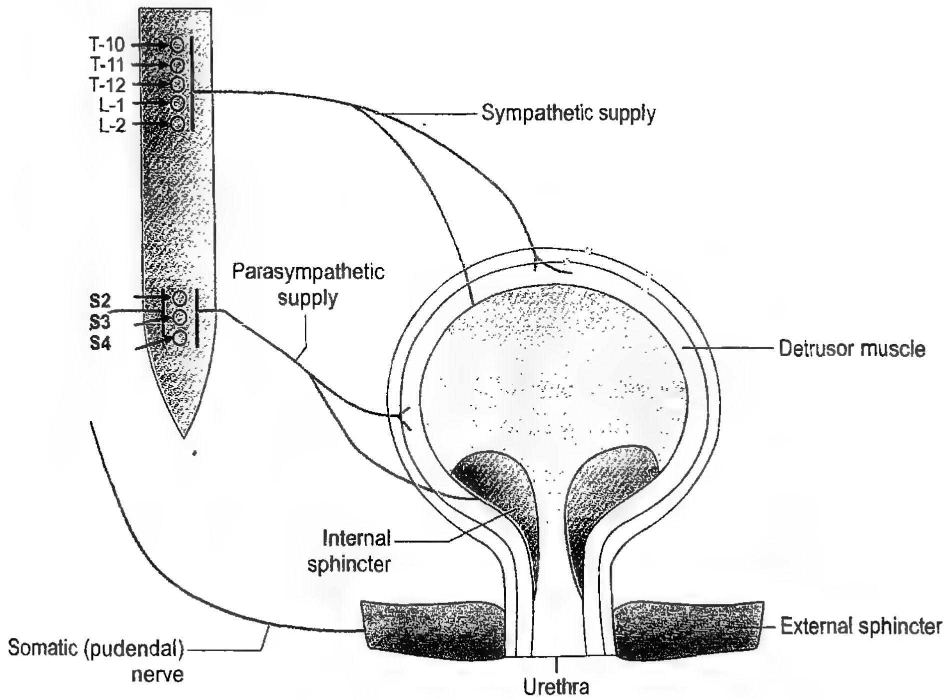

Fig. 5.10: Nerve supply of urinary bladder

- Bladder volume is typically normal or small, and involuntary contractions occur. Decreased bladder volume results in increased frequency of micturition. Involuntary contractions result in urgency and incontinence of urine.
- Bladder contraction and external urinary sphincter relaxation are typically uncoordinated (detrusor-sphincter dyssynergia) resulting in failure of external sphincter to relax when bladder is contracting which leads to incomplete emptying.

Central Lesion

- Disease involving the superior frontal and anterior cingulate gyri cause loss of control of micturition. When the lesion is more anterior, the patient is not worried or embarrassed by the incontinence due to a disinhibition state.

Investigations

- Normal micturition can be studied by urodynamic studies which involves constant recording of intravesical and intraurethral pressure, and perineal floor EMG, with fluoroscopic monitoring. These urodynamic studies facilitate the diagnosis of neurogenic bladder dysfunction.
- MRI of the spinal cord can show any spinal cord lesions.

Treatment

- In urinary retention, bladder drainage by continuous indwelling catheter may be necessary. Since, continuous indwelling catheter can cause infection if kept for a long time, intermittent catheterisation may be necessary to prevent infection. Prophylactic antibiotics may be necessary. Parasympathomimetic drugs like carbachol and bethenocol cause contraction of the detrusor and are useful in flaccid paralysis of the bladder.
- In spastic paralysis, anticholinergics such as propantheline, which causes relaxation of the detrusor, may be tried.
- Surgery is a last resort. It is indicated in patients who cannot use continuous or intermittent bladder drainage. Sphincterotomy (for men) converts the bladder into an open draining conduit. Sacral (S3 and S4) rhizotomy converts a spastic into a flaccid bladder. Urinary diversion may involve an ileal conduit or ureterostomy.

Q. Mention the various forms of neurosyphilis.

Q. Describe the clinical features and management of meningovascular syphilis.

Q. General paresis of the insane.

Q. Tabes dorsalis.

- The term "neurosyphilis" refers to infection of the central nervous system (CNS) by *Treponema pallidum (T. pallidum)*. Many patients are able to clear the infection spontaneously or due to antibiotic therapy. Nowadays neurosyphils is mainly seen in HIV patients who are not able to clear the infection. Neurosyphilis can occur at any time after initial infection.
- Various forms of neurosyphilis are discussed as follows.

Early Forms

- Meningitis—involvement of the cerebrospinal fluid (CSF) and meninges.
- Meningovascular syphilis—involvement of meninges and vasculature.

Late Forms

- General paresis of the insane—involvement of brain parenchyma.
- Tabes dorsalis—involvement of spinal cord parenchyma.

Meningovascular Syphilis

- Just like any other bacterial meningitis, syphilitic meningitis can cause an infectious arteritis of any vessel in the subarachnoid space which results in thrombosis of the vessel leading to ischemia, and infarction of the brain.
- Patients may present as ischemic stroke. Clinical features depend on the vessel involved. Less commonly, anterior spinal artery can get involved leading to spinal cord infarction. The middle cerebral artery and its branches are most commonly affected. Meningovascular syphilis may develop in the first few months or years after the syphilis infection. Associated meningitis may manifest as headache, dizziness, or personality changes.
- CSF analysis shows increased cells with predominant lymphocytes and increased protein concentration. CSF-VDRL is usually but not always reactive. Angiography can demonstrate the narrowed or blocked vessels and neuroimaging shows one or more areas of infarction.

General paresis (general paralysis of the insane; paretic neurosyphilis; dementia paralytica)

- This is a progressive dementing illness due to involvement of the brain parenchyma by syphilis.
- General paresis usually develops 10 to 25 years after infection, but it can occur much earlier also.
- In the early stage, patients have forgetfulness and personality change. There is progressive decline in memory and judgment leading to severe dementia. There may be psychiatric symptoms such as depression, mania, or psychosis.

- Neurologic findings include dysarthria, facial and limb hypotonia, intention tremors of the face, tongue, and hands, and reflex abnormalities.
- CSF examination shows increased lymphocytes and protein. The CSF-VDRL is reactive in virtually all patients, and neuroimaging usually shows brain atrophy.

Tabes Dorsalis

- Tabes dorsalis (also called locomotor ataxia) is a disease of the posterior columns of the spinal cord and of the dorsal roots. It has the longest latent period between primary infection and onset (average of about 20 years). It is rare now due to availability of antibiotic therapy.
- Patient presents with sensory ataxia and sensory symptoms such as lancinating pains and paresthesias. There may be depressed lower limb reflexes, impaired vibratory and position sensation, impaired touch and pain, and optic atrophy.
- Sometimes gastric crises, characterized by recurrent attacks of severe epigastric pain, nausea, and vomiting may be seen.
- Pupillary irregularities are common and include Argyll-Robertson pupil (accommodation reflex present, light reflex absent).
- Other findings seen with tabes dorsalis include absent lower extremity reflexes.

Treatment of Neurosyphilis

- All forms of neurosyphilis are treated as follows.

Drugs of Choice

- Penicillin G3 to 4 million units IV every four hours or 24 million units per day continuous IV infusion for 10 to 14 days.

Alternatives

- Drug of choice for neurosyphilis is aqueous penicillin 3 to 4 million units IV q 4 h (best penetrates the CNS but may be impractical) or procaine penicillin G 2.4 million units IM once/day plus 500 mg probenecid po qid is recommended; both drugs are given for 10 to 14 days, followed by benzathine penicillin 2.4 million units IM once/week for 3 weeks. Alternative is ceftriaxone 2 g IV once daily for 10 to 14 days.
- Because *Treponema pallidum* cannot be cultured in the laboratory, success of neurosyphilis treatment should be monitored by resolution of clinical features and CSF abnormalities. CSF should be examined at three to six months after treatment and every six months thereafter until CSF white blood cell (WBC) count is normal and CSF-VDRL is nonreactive. The CSF WBC count should decline at six months after successful treatment, and all CSF abnormalities should resolve by two years after treatment. Failure to meet these criteria should prompt retreatment.

Q. Charcot's joint (neuropathic arthropathy).

- Charcot's joint is chronic, progressive, destructive arthropathy due to loss of sensation of a joint.
- It is seen in tabes dorsalis, syringomyelia, diabetic neuropathy and other sensory polyneuropathies.
- Hips, knees and ankles are most commonly involved.
- Lack of proprioception and pain sensation in the joints results in ligamentous laxity, increased range of joint movement, instability, and damage by minor trauma. Pain is minimal even though there may be extensive joint destruction.
- Treatment involves rest to the joint and avoidance of weight bearing in early stages. Bisphosphonates such as pamidronate and aledronate have been shown to be helpful in the treatment of Charcot's joints. In late stages when there is loss of joint architecture and deformities, surgery and orthotic support may help. Underlying cause should be tackled.

Q. Enumerate the causes of low backache.

Causes of Low Backache

Mechanical Problems

- Lumber strain
- Degenerative process of disks and facets
- Intervertebral disc prolapse
- Spinal stenosis
- Osteoporotic compression fracture
- Spondylolisthesis
- Traumatic fracture
- Congenital disease (severe kyphosis and scoliosis)
- Spondylolysis.

Nonmechanical Problems

- Neoplasia (multiple myeloma, metastatic carcinoma, lymphoma leukemia, etc).
- Infection (osteomyelitis, diskitis, paraspinal abscess and shingles).
- Inflammatory arthritis (ankylosing spondylitis and psoriatic spondylitis).
- Paget's disease of bone.

Visceral Disease

- Disease of pelvic organs (prostatitis, endometriosis and pelvic inflammatory disease).

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- Renal disease (nephrolithiasis, pyelonephritis and perinephric abscess).
- Aortic aneurysm.
- Gastrointestinal disease (pancreatitis, cholecystitis and penetrating ulcer).

Q. Discuss the etiology, clinical features, diagnosis and management of sciatica.

Q. Discuss the etiology, clinical features, diagnosis and management of intervertebral disc prolapse (IVDP).

Sciatica

- Sciatica is pain along the sciatic nerve. It usually results from compression of nerve roots in the lower back.

Etiology

- Disc herniations (L4-5 or L5-S1 interspace) (commonest cause)
- Neoplasms
- TB spine
- Spinal stenosis
- Entrapment neuropathy
- Myofascial pain syndromes
- Trochanteric bursitis
- Vascular malformations
- Endometriosis
- Diabetic radiculoneuropathy
- Herpes zoster (shingles)
- Idiopathic lumbosacral plexitis
- Entrapment of the sciatic nerve by the pyriformis muscle

Clinical Features

- The classic feature is aching pain in the buttock and paresthesias radiating into the posterior thigh and calf or into the posterior lateral thigh and leg.
- Straight leg raising (SLR) test (Lasegue's sign) is performed with the patient lying supine. The involved leg is raised straight up, while the ankle is kept at 90 degrees of flexion. Disc herniation tends to tether the irritated nerve roots; as a result, stretching the nerve roots with SLR causes reproduction and radiation of pain into the lower limb.
- There may be motor and sensory deficits in the lower limb depending on which nerve root is involved.
- Involvement of S1 root—leg pain is worse than back pain. Sensory impairement in S1 dermatome. Weakness of toe flexors and gastrocnemius, and rarely of hamstrings. Ankle jerk is diminished or absent.
- Involvement of L5 root—low back pain is worse than leg pain. Sensory impairement in L5 dermatome. Weakness in extensor hallucis longus, tibialis anterior, and peroneus muscles, leading to foot drop. There is usually no reflex loss
- Involvement of L4 or L3—low back pain is worse than leg pain. Pain radiates to corresponding dermatome. Sensory impairment may be present in the same dermatome. Weakness in the quadriceps and iliopsoas muscles. Diminished or absent knee jerk.

Investigations

- Plain X-ray of lumbosacral spine may detect osteoporosis, spondylosis, fractures or any other pathology.
- MRI of lumbosacral spine is the most useful investigation to know the cause of sciatica. It can show disc herniation and other lesions clearly.
- Nerve conduction velocity (NCV) studies are also useful to detect the nerve root involved and the type of pathology.

Treatment

- Many patients recover without the need for invasive interventions such as surgery. Patients should be advised to continue their regular activities and avoid strenuous or heavy lifting. Bed rest is unnecessary unless the deficits are severe, because bed rest can actually prolong the recovery time.
- Analgesics (NSAIDs, paracetamol) can be used to control pain if necessary. The analgesic should be taken on a regular schedule (up to 6 weeks) rather than on demand.
- Drugs that decrease neuropathic pain such as gabapentin or other anticonvulsants or low-dose tricyclic antidepressants (amitryptaline) may relieve symptoms. Gabapentin 100 to 300 mg at bedtime is used along with analgesics.
- Surgery may be required in patients with intractable pain and neurological deficits. Surgical procedures are laminectomy, microdiscectomy, spinal fusion and lumbar disc replacement.

Q. Discuss the pathology, clinical features, diagnosis and management of cervical spondylosis.

- Cervical spondylosis is a degenerative condition of the cervical spine.

Pathology

- Degenerative changes take place in both the intervertebral disc and vertebral bodies.
- Disc degeneration leads to herniation of nucleus pulposus. Posterior herniation leads to compression of the spinal cord and lateral herniation leads to compression of nerve roots.

- Vertebral bone degeneration leads to bone overgrowth and osteophyte formation. Osteophytes on the posterior aspect lead to compression of the anterior aspect of the cord. Lateral osteophytes can encroach intervertebral foramina and compress nerve roots. Anterior osteophytes can compress esophagus and produce dysphagia.
- Compression of roots, cord or both leads to radiculopathy, myelopathy or myeloradiculopathy respectively.

Clinical Features

- Patient usually complains of neck pain which probably originates in the disc and spine.
- The range of neck movement is reduced, particularly rotation and lateral movement.
- Nerve root compression (radiculopathy) leads to pain radiating to tips of the shoulder, arm, forearm and even fingers. Pain is worsened by neck movement, coughing, sneezing or straining. There may be motor weakness, wasting of muscles and sensory impairment depending on the roots compressed.
- Sometimes L-hermitte's sign or 'barber's chair sign' (tingling in all four limbs or electric shock-like feelings down the back on flexing the neck) may be present.
- If the spinal cord is compressed (compressive cervical myelopathy) there is progressive spastic paraparesis, sensory impairment with a level, and bladder and bowel involvement.
- In some cases, clinical features of both radiculopathy and myelopathy are present (radiculomyelopathy).
- Vertebrobasilar insufficiency due to narrowing of vertebral artery foramina may produce vertebrobasilar ischemia, manifesting as brainstem signs like vertigo, tinnitus, ataxia and intermittent blurring of vision.
- Anterior osteophytes can compress esophagus and produce dysphagia.

Investigations

- *X-ray of the cervical spine*: Shows loss of natural cervical curvature, reduction of intervertebral spaces, osteophytes and narrowing of the cervical canal.
- *MRI of cervical spine*: This is the best investigation. It can show disc herniation, root compression and other soft tissue details accurately.

Treatment

- *Conservative treatment*: This includes analgesics and nonsteroidal anti-inflammatory agents, cervical traction, physiotherapy (short-wave diathermy, ultrasonic irradiation, static and dynamic neck exercises) and cervical collar to reduce neck movements.
- *Surgery*: If there is intractable root pain, foraminotomy can reduce the pain. In compressive myelopathy, surgical decompression or removal of spondylotic bars with or without spinal fusion can be used in selected cases.

Q. What are the diseases affecting posterior columns?

Q. What are the sensations carried by posterior columns? Mention the physical signs of posterior column lesion.

Diseases Affecting Posterior Columns

- Subacute combined degeneration
- Tabes dorsalis
- Compressive and non-compressive myelopathies.

Sensations carried by Posterior Columns

- Vibration
- Joint position sense (proprioception)
- Fine touch

Physical Signs of Posterior Column Lesion

- Sensory ataxia.
- Positive Romberg's sign.
- Impaired fine touch, vibration and joint postion sense.

Q. Romberg's sign.

- Romberg's sign is positive in sensory ataxias. It is not a test to assess the cerebellar function.

How to Elicit Romberg's Sign?

- Ask the patient to stand with the feet together. Then ask the patient to close both the eyes. If the patient shows swaying or loses balance, then Romberg's sign is positive. (Note: If the patient cannot stand with the feet together and eyes open, then a cerebellar lesion is present and Romberg's test is not applicable.)

Physiological Basis of Romberg's Sign

- To maintain equilibrium, a person requires intact joint position sense, intact vision, and intact vestibular and cerebellar systems. The absence of one can be compensated by the other. In posterior column leisons, joint position sense is lost, but the person maintains balance by visual compensation. When the eyes are closed, visual cue is removed and the person sways or loses balance.

Common Causes of Positive Romberg's Test

- Vitamin B_{12} deficiency—subacute combined degeneration of the cord.

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- Diabetic peripheral large fiber neuropathy
- Friedrich's ataxia
- Tabes dorsalis.

Q. Discuss the etiology, clinical features, diagnosis and management of subacute combined degeneration.

- Subacute combined degeneration is a nutritional disorder of the CNS due to vit B_{12} defficiency. There is degeneration of the dorsal and lateral spinal (corticospinal) columns, hence called combined degeneration. Degeneration is due to a defect in myelin formation of unknown mechanism.

Clinical Features

- It is subacute in onset.
- Posterior column degeneration produces paresthesias and ataxia associated with loss of vibration and position sense. Romberg's sign is positive.
- Corticospinal tract degeneration produces weakness, spasticity, extensor plantar response, clonus, paraplegia, and even fecal and urinary incontinence.
- Ankle jerk may be absent due to associated peripheral neuropathy but knee jerk is brisk.
- Other neurologic findings include memory loss, irritability, and dementia.
- There may be macrocytic anemia due to vit B_{12} defficiency.

Investigations

- Serum vit B_{12} level will be low.
- CBC usually shows megaloblastic anemia.
- MRI of the spinal cord and brain may show hyperintense lesions in the white matter.

Treatment

- Inj vit B_{12} (intramuscular) 1 mg every day for one week, followed by 1 mg every week for four weeks and then, 1 mg every month for the remainder of the patient's life.

Q. Discuss the classification, etiology, clinical features, diagnosis and management of motor neuron disease (MND).

Q. Amyotrophic lateral sclerosis (ALS).

Q. Progressive muscular atrophy (PMA).

- Motor neurone diseases (MNDs) are a group of degenerative disorders selectively affecting upper or lower motor neurons, or both. The condition is progressive and has a fatal outcome.
- Symptoms vary in severity and include muscle weakness and atrophy, fasciculations, emotional lability, and respiratory muscle weakness.
- MND has worldwide distribution. Males are affected more commonly and generally it starts between 45 and 60 years.

Types of Motor Neuron Diseases

- Amyotrophic lateral sclerosis (ALS)
- Spinal muscular atrophy (progressive muscular atrophy)
- Bulbospinal muscular atrophy (Kennedy's syndrome)
- Primary lateral sclerosis (PLS)
- Multifocal motor neuropathy with conduction block
- Poliomyelitis
- Familial spastic paraplegia (FSP).

- Amyotrophic lateral sclerosis (ALS) is the classical prototype of MND. ALS is the commonest type of MND, affecting the anterior horn cells (responsible for LMN signs) and the corticospinal tract (responsible for UMN signs). Other motor neuron diseases involve only particular subsets of motor neurons. Thus, bulbar palsy and spinal muscular atrophy involve the lower motor neurons of brainstem and spinal cord respectively. Primary lateral sclerosis (PLS) and familial spastic paraplegia (FSP) affect only upper motor neurons innervating the brainstem and spinal cord. The death of the motor neurons leads to atrophy of the muscles innervated by them.
- In motor neuron disease, sensory system, cerebellum and other areas of the brain are not affected. Motor neurons supplying eye muscles are also not affected.

Amyotrophic Lateral Sclerosis (ALS)

Etiology

- Most of the ALS cases are sporadic. Some are familial. Even sporadic cases may have some genetic influence. Following are risk factors for the development of ALS.
  - Genetic factors
  - Smoking
  - Old age
  - *Toxins*: Lead, tin and mercury
  - Electric shock
  - Radiation exposure
  - Excess glutamate activity

Pathology

- The main pathology is death of anterior horn cells of the spinal cord and cranial motor nuclei of the lower brainstem (except those that innervate ocular muscles). The pyramidal tracts show degenerative changes and there may be secondary demyelination.

Clinical Features

- Initial symptom is usually insidious onset of weakness and clumsiness of one hand for skilled activity which progresses and gross activity also becomes difficult.
- Overtime the opposite hand is involved and whole of both upper limbs may be affected.
- LMN signs such as wasting, flaccidity, loss of tendon reflexes and fasciculations are seen along with UMN signs such as spasticity and exaggerated reflexes.
- Lower limb involvement may precede or follow upper limb involvement. There is difficulty in walking with spastic gait and pyramidal signs. The knee and ankle jerks are exaggerated. Plantar response is extensor bilaterally.
- Involvement of cranial nerve nuclei (mainly IX, X, XI and XII) causes difficulty in swallowing, nasal regurgitation and slurred speech. Tongue shows atrophy and fasciculations. UMN involvement results in pseudobulbar palsy with exaggerated jaw jerk.
- There is no sensory loss but subjective sensations like numbness, cramps, neuralgic pain may be complaned of. Impotence occurs early in the disease. There is no loss of sphincter control.
- The progression of the disease is variable. It can be rapid and result in death within a year or it may be slow over many years. Death occurs due to respiratory failure.

Treatment

- So far, there is no effective drug for the treatment of MND.
- The drug riluzole has been approved for ALS because it produces a modest lengthening of survival. Riluzole blocks release of glutamic acid and may slow the progression of disease by disrupting glutamate-mediated neurotoxicity. There are many drugs currently under trial for MND.
- In the absence of specific therapy for MND, rehabilitation measures are helpful. Foot-drop splints facilitate walking and finger extension splints can potentiate grip. If there is difficulty in chewing and swallowing, gastrostomy is helpful for restoring nutrition and hydration.

Spinal Muscular Atrophy (Progressive Muscular Atrophy)

- Spinal muscular atrophies (SMA) include several types of hereditary disorders characterized by skeletal muscle wasting due to progressive degeneration of anterior horn cells in the spinal cord and of motor nuclei in the brain stem.
- SMA can begin in utero, during infancy, in childhood, or in adulthood.

Etiology

- SMA usually result from autosomal recessive mutations of a single gene locus on the short arm of chromosome 5. In addition to this, many other genetic defects have been demonstrated. There are many types of SMAs, common types are infantile SMA (Werdnig-Hoffmann disease) and adolescent SMA (Kugelberg-Welander disease).

Pathology

- There is degeneration of anterior horn cells of spinal cord and cranial nerve nuclei with atrophy and wasting of corresponding skeletal muscles.

Clinical Features

- SMA can start any time. There is flaccid weakness, hypotonia, decreased or absent deep tendon reflexes, fasciculations, and muscle atrophy. Young children may not be able to walk. Death occurs due to respiratory muscle weakness and respiratory failure.
- There is no sensory involvement.

Diagnosis

- Diagnosis of SMA is made by genetic testing in a patient with appropriate clinical features. Electromyogram and muscle biopsy reveal evidence of denervation but are unnecessary if a molecular diagnosis is established.

Treatment

- No treatment is currently available. Patients may benefit from physiotherapy, and other supportive care.
- Trials with ciliary neurotrophic factor, brain-derived neurotrophic factor, gabapentin, and riluzole are going on.

Q. Discuss the classification, etiology, clinical features, diagnosis and management of peripheral neuropathy.

Q. Mention the causes of polyneuropathies. Discuss the clinical features, diagnosis and management of polyneuropathies.

- The peripheral nervous system extends from the anterior horn cell or the sensory ganglion up to the neuromuscular junction or the receptors.
- Peripheral neuropathy is a general term and refers to any disorder affecting peripheral nervous system.
- Polyneuropathy is a specific term which refers to a generalized, symmetrical process affecting many peripheral nerves, with the distal nerves affected more prominently. Polyneuropathy is a type of peripheral neuropathy.

Table 5.20 Classification of peripheral neuropathies

Type	Features	Causes
Mononeuropathy	Pathological process a affecting a single nerve	Trauma, tumor, carpal tunnel syndrome affecting median nerve.
Mononeuritis multiplex (multiple mononeuropathy, or multifocal neuropathy)	Affects 2 or more discrete nerves in separate areas	Leprosy, diabetes, sarcoidosis, HIV, Polyarteritis nodosa
Polyneuropathy	Refers todiffuse, symmetrical disease, usually beginning peripherally. They are classified broadly into demyelinating and axonal types. The polyneuropathies can be acute or chronic, motor or sensory or sensorimotor (i.e. mixed) and autonomic	Guillain-Barré syndrome, diabetes mellitus
Monoradiculopathy	Single spinal root is affected	Disc prolapse, trauma, tumor
Polyradiculopathy	Many spinal roots are affected	Spondylosis, arachnoiditis, GB syndrome
Plexopathy	Brachial or lumbosacral plexus are affected	Diabetes, trauma, tumors

Polyneuropathy

Causes of Polyneuropathy

- **Metabolic**: Diabetes mellitus, amyloidosis, porphyria, paraproteinemia, hypothyroidism
- **Toxic:** Alcohol, lead, arsenic, thallium
- **Drugs:** Vincristine, INH, hydralazine, dapsone, amiodarone
- **Infections:** Leprosy, diphtheria, HIV, Lyme disease
- **Collagen disorders:** SLE, polyarteritis nodosa, rheumatoid arthritis
- **Vitamin deficiencies:** B_1, B_6, B_{12}
- **Paraneoplastic:** Carcinoma bronchus
- **Genetic:** Charcot-Marie-Tooth disease
- **Autoimmune:** Guillain-Barré syndrome (AIDP)
- Idiopathic

Clinical Features

- In polyneuropathy, Injury tends to be related to axon length; thus, longer axons are affected first, resulting in symptoms that begin in the lower extremities. Sensory symptoms usually precede motor symptoms.
- Patients present with slowly progressive sensory loss and dysesthesias such as numbness, a burning sensation and pain in the feet, and mild gait abnormalities (due to proprioceptive loss). As the syndrome progresses, mild weakness of the lower legs and hand symptoms may begin, resulting in the classic "glove and stocking" sensory loss. The numbness may continue to extend proximally in severe cases, affecting the intercostal nerves.
- GBS affects predominantly motor nerve fibers; thus, weakness rather than sensory loss is seen.
- Examination usually reveals distal loss of sensation to pin prick, light touch, vibration, cold, and proprioception. Reflexes are hypoactive or absent distally, usually at the ankles initially. Muscle weakness may be present in advanced neropathies.

Investigations

- *Electrodiagnostic testing*: Electromyography/nerve conduction studies (EMG/NCS) can determine whether it is axonal or demyelinating in character. Demyelinating disorders are characterized by slow nerve conduction velocity whereas axonal neuropathies are characterized by reduced amplitude of action potentials with relative preservation of the nerve conduction velocity.
- *Nerve biopsy*: Nerve biopsy is occasionally useful for diagnosing the underlying etiology of polyneuropathy such as amyloid. The sural nerve at the ankle is the preferred site for cutaneous nerve biopsy.
- *Other tests*: A standard laboratory "screen" in patients with polyneuropathy includes a complete blood count, ESR, TSH, serum protein electrophoresis, blood glucose, vitamin B_{12} concentration, antinuclear antibody, and urinalysis. Additional testing may include lumbar puncture, genetic testing, and muscle or nerve biopsy.

Treatment

- The aim of treatment is correcting the underlying cause and control of symptoms.
- *Treatment of the underlying cause*—proper control of diabetes, reducing exposures to toxins, withdrawing the causative drug, etc.
- *Treatment of symptoms and prevention of complications*—gabapentin, tricyclic antidepressants, and carbamazepine can be used to control neuropathic symptoms such as pricking pain and burning sensation. Physiotherapy, use of ankle-foot orthoses, splints, and walking assistance

devices can significantly improve lifestyle in the face of significant disability. Proper foot and nail care is important to prevent ulcer formation.

Q. Describe the etiology, clinical features, diagnosis and management of Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy-AIDP).

- The Guillain-Barré syndrome (GBS) is an acute monophasic illness causing a rapidly progressive polyneuropathy with weakness or paralysis.

Etiology and Pathogenesis

- Guillain-Barré syndrome (GBS) results from an immune response to a preceding infection that cross-reacts with peripheral nerve components because of molecular mimicry.
- The immune response can be directed towards the myelin or the axon of peripheral nerve, resulting in demyelinating and axonal forms of GBS.
- Many infections can trigger GBS. Commonly implicated infections are *Campylobacter jejuni* infection, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus (HIV). Other triggering events are immunization (influenza, meningococcal, etc), surgery, trauma, and bone marrow transplantation.
- Nerve damage is due to activated T cells and circulating antibodies such as antimyelin antibodies.

Subtypes of Guillain-Barré Syndrome (GBS)

Acute Inflammatory Demyelinating Polyneuropathy (AIDP)

- Demyelinating type. Recovery is rapid.

Acute Motor Axonal Neuropathy (AMAN)

- Axonal type. There is no sensory nerve involvement and no peripheral nerve demyelination. Recovery is rapid.

Acute Motor Sensory Axonal Neuropathy (AMSAN)

- Axonal type. Both sensory and motor fibers are affected and recovery is slow.

Miller-Fisher Syndrome (MFS)

- Demyelinating type. Characterized by ophthalmoplegia, ataxia and areflexia without significant limb weakness.

Clinical Features

- The cardinal features of GBS are progressive, symmetric muscle weakness and absent or depressed deep tendon reflexes. Weakness can vary from mild weakness of legs to complete paralysis of all extremity, facial, respiratory, and bulbar muscles.
- Weakness usually starts in the lower limbs, and then ascends up to involve trunk and upper limbs (ascending paralysis). However, in some patients weakness can begin in the arms or facial muscles and then descend down to involve trunk and lower limbs (descending paralysis).
- Severe respiratory muscle weakness may lead to respiratory failure and requires ventilatory support.
- Facial (LMN type) and oculomotor nerve involvement occur in some patients. Bilateral facial palsy also can occur.
- Sensory symptoms such as paresthesias occur in the hands and feet in most of the patients, but usually there are no objective sensory deficits. There is often prominent severe pain in the lower back.
- Autonomic neuropathy occurs in majority of patients and manifests as tachycardia, urinary retention, fluctuating BP, orthostatic hypotension, bradycardia, arrhythmias, ileus, and loss of sweating.
- GBS usually progresses over a period of about two weeks and recovery starts after about a month.

Investigations

- *Nerve conduction studies (NCS) and electromyography (EMG)* are used to confirm the diagnosis and also to know the type of GBS. Abnormalities in NCS that are consistent with demyelination are delayed distal latencies, slowed nerve conduction velocities, conduction block, etc. In case of axonal damage, needle EMG will show decreased recruitment and rapid firing motor units in weak muscles.
- *CSF analysis*: Protein is elevated with a normal WBC count. This is known as albuminocytologic dissociation, and is present in most patients one week after the onset of symptoms. However, cell count may be increased in patients with HIV infection.
- *Antibodies*: Against nerve components can be detected in the blood of GBS patients. However, antibody testing is not routinely used.

Treatment

- ***Plasmapheresis*** removes the circulating antibodies and helps in fast recovery. 4 sittings of plasmapheresis are recommended.
- ***Intravenous immune globulin (IVIG)*** probably acts by neutralizing circulating antibodies and immunomodulation. IVIG is given in a dose of 0.4 g/kg daily for 6 days.
- Both plasmapheresis and IV immunoglobulins have equal efficacy and combining both of them is not better than any one given alone.

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- *Steroids*—IV methyl prednsolone (1 gm IV infusion daily for 5 days) used to be popular earlier, but studies have shown that it does not provide any benefit in GBS.
- *Supportive therapy*—bowel and bladder care, adequate nutrition, monitoring for respiratory failure and providing ventilatory support if required, cardiac monitoring, and physiotherapy are all important.

Q. Differentiation between demyelinating and axonal neuropathy.

Table 5.21 Differentiation between demyelinating and axonal neuropathy

Features	Demyelinating neuropathy	Axonal neuropathy
Onset	Usually acute	Insidious
Sensory loss	Minimal	Significant (glove and stocking type)
Muscle wasting	No	Yes
Fasciculations	No	Yes
Reflexes	Loss of all deep tendon reflexes	Loss of only distal reflexes such as ankle
Recovery	Rapid and usually complete	Slow with residual deficit
CSF protein	Raised	Normal
Nerve conduction velocity	Very slow	Normal or slightly slow
Amplitude of action potential	Normal	Reduced

Q. Causes of peripheral neuropathies with significant autonomic neuropathy.

- Diabetes mellitus
- Hansen's disease
- Acute intermittent porphyria
- Alcoholism
- Guillain-Barré syndrome
- Amyloidosis
- *Inherited*: Riley-Day syndrome, Refsum's disease
- *Toxic neuropathies*: Thallium, acrylamide

Q. Carpal tunnel syndrome.

- Carpal tunnel syndrome (CTS) is entrapment neuropathy of median nerve in carpal tunnel of the wrist.
- This is the most common nerve entrapment disorder. Median nerve dysfunction occurs due to pressure on it within the carpal tunnel.

Causes

- Idiopathic
- Colles' fracture or other wrist trauma
- Hypothyroidism
- Diabetes mellitus
- Pregnancy (third trimester)
- Obesity
- Rheumatoid arthritis (with wrist involvement)
- Acromegaly
- Amyloidosis
- Renal dialysis patients

Clinical Features

- Pain and paresthesia in the thumb, first two fingers, and the radial-half of the ring finger (the distribution of the median nerve). Pain may radiate proximally into the forearm. Many patients experience pain at night and are awakened by abnormal sensations.
- Physical examination may reveal weakness of thenar muscles and flattening of the thenar eminence. There may be sensory loss in the palm and radial three-and-a-half fingers.
- Tinel's sign and Phalen's tests are often positive. Tinel's sign is elicited by tapping the flexor aspect of the wrist: this causes tingling and pain. In a positive Phalen's test, symptoms are reproduced on maximal wrist flexion for 1 minute.
- Nerve conduction studies (NCS) can show delayed conduction through median nerve at the wrist.

Treatment

- For mild cases, conservative measures such as, wrist splint at night, oral or local steroid injection, physiotherapy, and yoga can give relief. In pregnancy (fluid retention), it is often self-limiting.
- Surgical decompression of the carpel tunnel is required for severe cases.

Q. Meralgia paresthetica.

Meralgia paresthetica is the term used to describe the clinical syndrome of pain and paresthesia in the antero-lateral thigh due to compression of lateral femoral cutaneous nerve of thigh as it courses under inguinal ligament.

Etiology

- Entrapment and compression of the lateral femoral cutaneous nerve can occur due to following reasons.
- Obesity
- Tight garments around the waist
- Scar tissue near the lateral aspect of the inguinal ligament
- Pregnancy
- Diabetes
- Seat belt injuries

Clinical Features

- Tingling, numbness and burning pain over the anterolateral thigh is the classic presentation.
- The discomfort is often worsened by activities which increase intra-abdominal pressure such as coughing and Valsalva maneuvers.
- There may be sensory loss in the area of lateral femoral cutaneous nerve.

Treatment

- Meralgia paresthetica is a self-limited, benign condition. Reassure the patient that it is not a serious problem. Advice the patient to lose weight if obese and to avoid tight garments and belt.
- In patients with persistent pain inspite of all these measures, drugs like carbamazepine or phenytoin, or gabapentin can be helpful in reducing neuropathic pain.
- Local corticosteroid injections can be used occasionally to control symptoms.
- Rarely, surgery is necessary. Decompression of the nerve (sectioning the inferior slip of the attachment of the inguinal ligament to the anterior superior iliac spine) may provide long lasting relief in some.

Q. Mention the diseases affecting neuromuscular junction.

Q. Describe the etiology, pathophysiology, clinical features, investigations and management of myasthenia gravis.

Q. Cholinergic crisis.

Q. Myasthenic crisis.

Diseases affecting neuromuscular junction are:

Autoimmune
- Myasthenia gravis
- Eaton-Lambert syndrome – "LEMS"

Toxic
- Botulism
- Drug induced
- Organophosphate poisoning

Congenital
- Congenital myasthenic syndrome
- Familial limb girdle myasthenia

Myasthenia Gravis

- Myasthenia gravis is an immunologically mediated disorder affecting neuromuscular transmission. It is characterised by fluctuating muscle weakness worsened by repetitive use, and improved by resting.

Etiology and Pathology

- The basic abnormality in myasthenia gravis is at the neuromuscular junction. Muscle weakness is due to an antibody-mediated, T cell dependent immunological attack directed at postsynaptic acetylcholine receptors. Antibodies bind to acetylcholine receptors and prevent acetylcholine action leading to weakness.
- There is a strong association between HLA B8 antigen and myasthenia gravis.
- Thymus plays an unknown role in the pathogenesis. There is an increased incidence of myasthenia gravis in patients with thymoma.

Clinical Features

- The disease occurs at all ages. Usually it starts between 10–70 years of age. Onset may be sudden or gradual.

* ♂ > ♀ (Autoimmune)

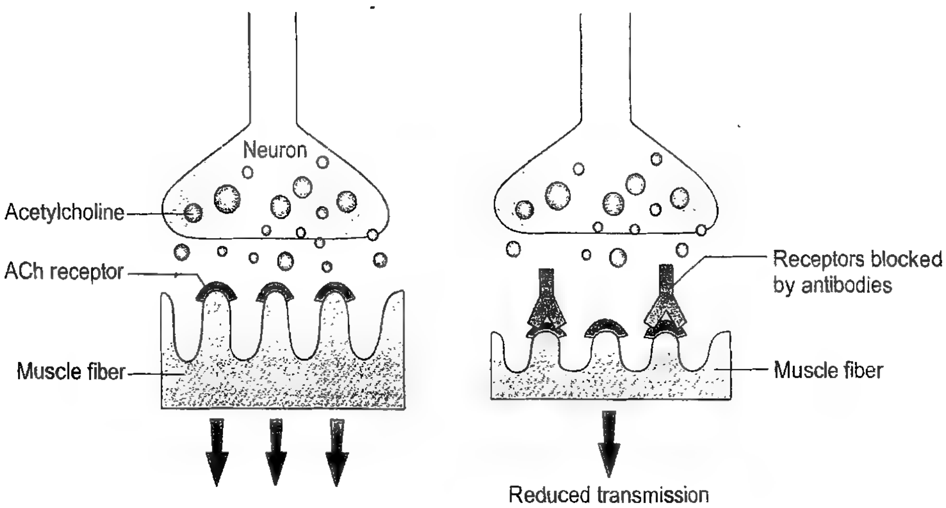

Fig. 5.11: Normal NMJ (left) and abnormal NMJ in myasthenia gravis (right)

Screening test

- It is two times more common in women.
- The characteristic feature of weakness in myasthenia gravis is its fluctuation. Muscle strength decreases with activity and improves with rest. Patients complain of easy fatigability. This can be demonstrated by asking the patient to look up without closing the eyes for a minute, count loudly from 1 to 100, and hold the arms in a horizontal position for a minute. Muscle wasting does not occur. Tendon reflexes are preserved. Smooth muscles are not involved.
- The extra-ocular muscles get involved first in most cases because of which patient complains of diplopia. Weakness of levator palpebrae superioris leads to ptosis.
- Involvement of facial muscles results in difficulty in eye closure, inability to whistle and a distorted smile. There is difficulty in chewing tough foods. Weakness of the pterygoids results in difficulty in closing the mouth, and the jaw may hang. Weakness of bulbar muscles results in difficulty in swallowing and speaking. Voice becomes low and fades away as the patient continues to speak.
- In the limbs proximal muscles are commonly involved than distal ones. This results in difficulty in raising the arms above the shoulders, difficulty in getting up from squatting position or climbing stairs.
- Involvement of intercostal muscles and diaphragm leads to respiratory difficulty.
- There may be other autoimmune diseases such as, rheumatoid arthritis, pernicious anemia, systemic lupus erythematosus, etc.

Diagnosis

- Fluctuating weakness is characteristic of myasthenia gravis. Weakness increases on exertion and improves on resting. The combination of ptosis, ophthalmoplegia with weakness of orbicularis oculi and normal pupils is virtually diagnostic.

smooth mls (N)

Investigations

Anticholinesterase Tests

- Drugs which inhibit acetylcholinesterase can increase the levels of acetylcholine at the neuromuscular junction and improve muscle weakness. Such drugs include edrophonium and neostigmine.
- *Neostigmine test*: 1 mg of neostigmine is given intramuscularly or subcutaneously. Muscle weakness improves in 15–20 minutes and reaches its peak in 30 minutes. 1 ampoule atropine (0.6 mg) can be given before injecting neostigmine to prevent muscarine side-effects and cardiac complications of neostigmine.
- *Edrophonium (Tensilon) test*: Edrophonium is a short-acting anticholinesterase drug. 10 mg is drawn into a syringe. Initially 2 mg is injected IV and if there are no side-effects the balance 8 mg is given after 30 seconds. Muscle weakness improves within a minute and the effect lasts for 5–10 minutes. Atropine can be given before injecting edrophonium to prevent side effects.

Electromyography

SFEMG – jitter – most sn test

- Supramaximal stimulation of a motor nerve at 2 to 3 Hz results in decrement of the amplitude of the evoked muscle action potential from the first to the fifth response. The test is positive in nearly all patients. The abnormality, i.e. decremental response, is reversed by neostigmine.

Serologic Tests

– Most specific

- The demonstration in serum of antibodies against ACh receptors is a sensitive diagnostic test. Patients with pure ocular myasthenia may not have ACh receptor antibodies.

50% – Ocular MG
85% – Generalized MG.

Other Tests

- A chest X-ray should be taken to rule out any associated thymoma. Thymic tumor would be seen as an anterior mediastinal mass. CT-scan is more sensitive for detecting thymic enlargements.
- Thyroid function tests should be done as 10% of cases have associated hyperthyroidism.

3–7% → Hypothyroidism

Treatment

Augmentation of Neuromuscular Transmission

- Anticholinesterases are the most commonly used drugs. These are pyridostigmine and neostigmine. Pyridostigmine has fewer muscarinic side effects and is therefore more widely used. In patients who do not respond adequately to anticholinesterases, other forms of therapy should be added.

Immune Suppression

- Alternate-day prednisolone treatment induces remission or significantly improves the disease (dose 1mg/kg body weight). After the improvement reaches a plateau, the dose must be lowered gradually over several months to establish the minimum maintenance dose.
- Azathioprine in doses of 2 to 3 mg/kg/day also induces remissions or provides improvement. Azathioprine along with prednisolone reduces the dose of prednisone and is associated with fewer treatment failures, longer remissions, and fewer side effects than either drug alone. Cyclosporine or mycophenolate mofetil can be used in patients who are refractory to prednisolone and azathioprine.

Other Treatments

- Plasmapheresis is indicated in severe generalized or fulminating myasthenia gravis that is refractory to other forms of treatment. Intravenous immunoglobulin therapy is also useful in severe myasthenia gravis.
- Thymectomy increases the remission rate and improves the clinical course of myasthenia gravis.

Cholinergic and Myasthenic Crisis

- *Cholinergic crisis* is due to overtreatment with anticholinesterase drugs (pyridostigmine and neostigmine). There is increased availability of ACh leading to persistent depolarization of neuromuscular junction and hence weakness. Typically weakness worsens despite giving increasing amounts of anticholinesterase drugs. Cholinergic crises are associated with muscarinic effects, such as abdominal cramps, nausea, vomiting, diarrhea, miosis, lacrimation, increase in bronchial secretions, diaphoresis, and bradycardia.
- *Myasthenic crisis* is due to severe worsening of myasthenia gravis. There are no muscarinic symptoms. Injection of 2 mg edrophonium (tensilon) given intravenously improves weakness in myesthenic crisis whereas weakness worsens if it is cholinergic crisis. However, in practice, the two types of crises may be difficult to distinguish. Both types of crisis have difficulty with respiration, feeding, or handling of secretions and are best treated by drug withdrawal, endotracheal intubation or tracheostomy, ventilator support and IV fluids.

Q. Eaton-Lambert myasthenic syndrome.

- Eaton-Lambert myasthenic syndrome is an autoimmune disease where antibodies destroy calcium channels at the motor nerve terminal. This leads to decreased presynaptic release of acetylcholine at the neuromuscular junction causing muscle weakness.
- It is usually associated with small cell carcinoma of the lung.
- It is more common in males and commonly occurs after the age of 50 years.
- Patient complains of weakness and fatigability more often in the legs with relative sparing of extraocular and bulbar muscles. Weakness may improve after a few seconds of activity (opposite of myasthenia gravis which worsens after activity). Autonomic symptoms may occur. Deep tendon reflexes are depressed or absent.
- EMG shows incremental response to repetitive stimulation.
- Treatment consists of removal of tumor if detected, immunosuppression, and enhancement of neuromuscular transmission by guanidine and 3, 4 diaminopyridine.

Q. What is myopathy? Classify myopathies.

- The term *myopathy* refers to muscle diseases in which there is a primary structural or functional impairment of muscle.
- Myopathies therefore do not include diseases of the central nervous system (CNS), lower motor neurons (motor neuron disease), peripheral nerves, or neuromuscular junction which have secondary effects on muscles.

Classification of Myopathies

Hereditary
- Muscular dystrophies
- Congenital myopathies
- Myotonias and channelopathies
- Metabolic myopathies
- Mitochondrial myopathies

Acquired
- Inflammatory myopathies
- Endocrine myopathies
- Myopathies due to systemic illness
- Drug induced/toxic myopathies

Q. What are muscular dystrophies? Enumerate muscular dystrophies. Describe the etiology, clinical features and management of Duchenne's muscular dystrophy.

- Muscular dystrophies are inherited myopathies characterized by progressive muscle weakness and degeneration with subsequent replacement by fibrous and fatty tissue.

Types of Muscular Dystrophies

X-linked muscular dystrophy
- Duchenne
- Becker
- Emery-Dreifuss

Autosomal dominant
- Facioscapulohumeral (FSH)
- Oculopharyngeal - OP
- Myotonic

Autosomal dominant/recessive
- Limb-girdle

Sporadic
- Congenital

Duchenne Muscular Dystrophy

- Duchenne-type muscular dystrophy is an X-linked recessive disorder resulting from mutations of dystrophin gene located at Xp21.
- The incidence of Duchenne-type muscular dystrophy is 1 in 3500 male births.

5

Pathogenesis

- Dystrophin is a subsarcolemmal cytoskeletal protein which provides support to the muscle membrane during contraction.
- Dystrophin deficiency weakens the sarcolemma, permitting the influx of calcium-rich extracellular fluid, which then activates intracellular proteases and complement, leading to fiber necrosis.

Clinical Features

- Duchenne dystrophy presents as early as age 2 to 3 years.
- Proximal muscles are affected more severely (limb-girdle pattern).
- The affected child has difficulty running, jumping, and walking up steps. When arising from the floor, affected boys may use hand support to push themselves to an upright position (Gower's sign).
- Calf muscles may appear hypertrophied due to replacement of muscle fibers by fat (pseudohypertrophy).
- The disease is progressive and the child is usually wheelchair bound by the age of twelve.
- Paraspinal muscle weakness leads to progressive kyphoscoliosis.
- Respiratory function gradually declines. Most patients die of respiratory complications in their 20s.
- Cardiac muscle is also affected leading to dilated cardiomyopathy and conduction defects.
- The smooth muscle of the gastrointestinal tract is also involved, and intestinal pseudo-obstruction occurs.
- Children also frequently have varying degrees of mental retardation.

Investigations

- Dystrophin gene defect can be detected by DNA analysis. Muscle biopsy can show dystrophin deficiency, muscle fiber degeneration and replacement with connective tissue and fat.
- Serum creatine kinase (CK) levels may be elevated but decrease when there is severe loss of muscle mass.
- Electromyogram (EMG) shows fibrillation potentials and myopathic motor units.

Treatment

- Corticosteroids are the mainstay of treatment for Duchenne-type muscular dystrophy. Prednisolone 0.75 mg/kg/day can improve muscle strength and delay the progression into a wheelchair bound state. Prednisolone also delays respiratory compromise, but it cannot prevent deterioration and death.
- Gene therapy for muscular dystrophies is currently under evaluation.
- Stem cell therapy is also under investigation.

Becker Muscular Dystrophy

- The pathogenesis, investigations and treatment of Becker muscular dystrophy is same as that of Duchenne muscular dystrophy. Becker muscular dystrophy is a mild form compared to Duchenne and typically becomes symptomatic much later. Ambulation is usually preserved until at least age 15, and many children remain ambulatory into adulthood. Most affected children survive into their 30s and 40s.

Q. Causes of wasting of small muscles of hand.

- *Spinal cord lesions*: Motor neuron disease, syringomyelia, intramedullary tumours, C8, T1 leisons (cervical spondylosis, trauma)
- *Medial cord lesions of brachial plexus*: Pancoast tumor, metastases, trauma, thoracic outlet syndrome.
- *Median nerve lesions*: Trauma, carpal tunnel syndrome, vasculitis.
- *Ulnar nerve lesions*: Trauma, entrapment, leprosy, vasculitis
- *Muscle disease*: Focal amyotrophy.

Q. Wernicke's encephalopathy. “QoA”

Q. Korsakoff psychosis.

- Wernicke's encephalopathy (WE) is a common, acute neurologic disorder caused by thiamine deficiency.

Etiology

- Wernicke's encephalopathy usually occurs in chronic alcoholics. Excessive alcohol intake interferes with thiamin absorption from the GI tract and hepatic storage of thiamin.
- Wernicke's encephalopathy may also result from other conditions that cause prolonged undernutrition or vitamin deficiency (e.g. recurrent dialysis, hyperemesis, starvation, gastric plication, cancer, AIDS).
- Loading carbohydrates in patients with thiamin deficiency (i.e. refeeding after starvation or giving IV dextrose-containing solutions to high-risk patients) can trigger Wernicke's encephalopathy because remaining thiamine gets used up for carbohydrate metabolism and acute deficiency is precipitated.

Pathology

- Pathologically there is loss of neuronal processes, gliosis, and petechial hemorrhage in the medial thalamus and hypothalamus, midbrain periaqueductal gray matter, floor of the fourth ventricle and cerebellum.

Clinical Features

- Clinical features start suddenly.
- It is manifested by a clinical triad of encephalopathy, oculomotor dysfunction, and gait ataxia.
- Encephalopathy manifests as disorientation, indifference, inattention, drowsiness, or stupor. If patients are not treated, stupor may progress to coma and death.
- Oculomotor dysfunction causes horizontal and vertical nystagmus and partial ophthalmoplegias (e.g. lateral rectus palsy, conjugate gaze palsies).
- Gait ataxia results from vestibular disturbances and cerebellar dysfunction. Gait is wide-based and slow, with short steps.

Diagnosis

- Diagnosis is clinical and should be suspected in chronic alcoholics and malnourished patients.
- There is decreased level of erythrocyte transketolase. Thiamin levels are not routinely measured.
- Alternative pathologies should be ruled out by appropriate investigations such as CT brain, CSF studies, and blood investigations.

Treatment

- If Wernicke's encephalopathy is suspected, it should be treated immediately with parenteral thiamine 100 mg IV or IM, continued daily for at least 3 to 5 days.
- Mg is a necessary cofactor in thiamin-dependent metabolism, and hypomagnesemia should be corrected using Mg sulfate 1 to 2 g IM or IV q 6 to 8 h.
- Supportive treatment includes hydration, correction of electrolyte imbalances, and general nutritional therapy, including multivitamins.

Korsakoff's Psychosis

- Korsakoff's psychosis is a late complication of persistent Wernicke's encephalopathy and results in memory deficits, confusion, and behavioral changes.
- Almost 80% of untreated patients with Wernicke's encephalopathy develop Korsakoff's psychosis. Other triggers include head injury, subarachnoid hemorrhage, and thalamic lesions.

Clinical Features

- Immediate memory is severely affected; retrograde and anterograde amnesia occurs in varying degrees. Remote memory is less affected. Disorientation to time is common. Emotional changes are common; they include apathy, blandness, or mild euphoria with little or no response to events, even frightening ones. Spontaneity and initiative may be decreased.
- Confabulation is often a striking feature. Patients unconsciously fabricate imaginary or confused accounts of events they cannot recall.
- Features of both Wernicke's encephalopathy and Korsakoff's psychosis can coexist and is called Wernicke Korsakoff's syndrome.

Diagnosis

- Diagnosis is based on typical symptoms in patients with a history of alcohol abuse. Other causes of symptoms (e.g. CNS injury or infection) must be ruled out by appropriate investigations such as brain imaging and CSF studies.

Treament

- Treatment consists of thiamin and adequate hydration.

Q. Creutzfeldt-Jakob disease (CJD).

- Creutzfeldt-Jakob disease (CJD) is the most common prion disease in human beings.
- Most cases are sporadic, and acquired by eating meat from cattle with bovine spongiform encephalopathy (mad cow disease) or inoculation (e.g. after cadaveric corneal or dural transplants, use of stereotactic intracerebral electrodes, or use of growth hormone prepared from human pituitary glands). It usually affects middle-aged to elderly people.
- Pathologically, there is spongiform change, neuronal loss, and acumulation of the abnormal prion protein in the brain.

Clinical Features

- Rapidly progressive dementia, with myoclonus and a characteristic EEG pattern (repetitive slow wave complexes).
- Visual disturbance or ataxia.
- Death occurs after a mean of 4–6 months.

Diagnosis

- CJD should be suspected in elderly patients with rapidly progressive dementia, especially if accompanied by myoclonus or ataxia.
- MRI can show evolving patchy areas of hyperintensity in the cortical ribbon, which strongly suggest CJD.
- CSF analysis shows presence of proteins 14-3-3, brain-specific enolase, and tau.
- EEG shows characteristic periodic sharp waves in advanced disease.

Treatment

- There is no known treatment.

Q. Define hydrocephalus. Discuss the etiology, pathogenesis, investigations and management of hydrocephalus.

- Hydrocephalus is accumulation of excessive amounts of CSF, causing cerebral ventricular enlargement and increased intracranial pressure.
- The increased pressure distinguishes hydrocephalus from atrophy, where there is dilatation of ventricular system due to loss of brain tissue without increased CSF pressure.
- It can be either congenital or acquired from events during or after birth.

Etiology

- Hydrocephalus can result from
- Obstruction of CSF flow (obstructive hydrocephalus)
- Impaired resorption of CSF in the subarachnoid space (communicating hydrocephalus).

Causes of Hydrocephalus

Obstruction
- Chiari-2 type malformation
- Aqueductal stenosis
- Dandy-Walker malformation
- Tumors
- Colloid cyst
- Cerebellar abscess
- Cerebellar or brainstem hematoma

Impaired resorption
- Bacterial meningitis (especially tuberculous)
- Sarcoidosis
- Subarachnoid hemorrhage

Clinical Features

- The signs and symptoms of hydrocephalus are due to raised intracranial pressure (ICP) and dilatation of the ventricles.
- Small children may have increased head circumference.
- Affected patients may have changes in their personality and behavior such as irritability, indifference, and loss of interest.
- Headache, nausea, vomiting, bradycardia, and hypertension may be present due to raised ICP. Compression of the third or sixth cranial nerve may result in extraocular muscle pareses leading to diplopia.
- Fundoscopic examination may reveal papilledema.

Investigations

CT or MRI Scan Head

- Shows dilated ventricles and any associated CNS malformations or tumors.

Lumbar Puncture

- Useful to rule out an infection causing adhesive arachnoiditis or ependymitis. However, it is contraindicated if there is a space-occupying lesion such as an intracranial tumor or a brain abscess, because of the risk of cerebral herniation.

Treatment

Medical Therapy

- Includes the use of diuretics (furosemide and acetazolamide) and serial lumbar punctures. These are less effective than surgical therapy.

Surgical Therapy

- Diversion of the CSF by means of a shunt procedure between the ventricular system and the peritoneal cavity or right atrium may result in prompt relief of symptoms in obstructive or communicating hydrocephalus.

Q. Normal pressure hydrocephalus (NPH). "400"

- Normal pressure hydrocephalus (NPH) refers to a condition of pathologically enlarged ventricles with normal CSF pressure. It is thought to result from a defect in CSF resorption in arachnoid granulations.
- NPH is associated with a classic triad of dementia, gait disturbance, and urinary incontinence.
- It is most common in adults over the age of 60 years and affects both sexes equally.
- It improves after removing some CSF by lumbar puncture.
- Treatment involves repeated lumbar puncture to remove CSF or ventriculoperitoneal shunt operation.

Q. Acute confusional state (delirium).

- Delirium is an acute, transient, usually reversible, fluctuating disturbance in attention, cognition, and consciousness level.
- Delirium is sometimes called acute confusional state or toxic or metabolic encephalopathy.
- Causes of delirium include almost any disorder or drug.

Table 5.22 Causes of delirium

Brain disorders
- CNS infections (meningitis, encephalitis, cerebral abscess, subdural empyema)
- Intracerebral hemorrhage
- Subdural hematoma
- Subarachnoid hemorrhage
- Cerebral venous thrombosis
- Head injury (cerebral contusions)
- Postictal state

(contd.)

Table 5.22 Causes of delirium (*contd.*)

Infections
- Chest infection
- Urinary tract infection
- Septicemia

Endocrine disorders
- Hypo-/hyperthyroidism
- Adrenal disease
- Hyper-/hypoglycemia

Electrolyte imbalance
- Hyper-/hypocalcemia
- Hyponatremia

Systemic organ failure
- Cardiac failure
- *Liver failure*: Acute, chronic
- Respiratory failure (hypercarbia and hypoxemia)
- *Renal failure*: Acute, chronic

Toxins
- Alcohol intoxication/withdrawal
- Carbon monoxide
- Methanol
- Insecticides

Drugs
- Narcotics
- Cocaine
- Antichilinergics

Neoplastic
- Primary and secondary brain tumors

Physical disorders
- Burns
- Electrocution
- Hyperthermia
- Hypothermia

Pathophysiology

- Exact mechanism of delirium is not fully understood but may involve impairment of cerebral oxidative metabolism, neurotransmitter abnormalities, and generation of cytokines. Stress of any kind increases sympathetic activity and decreases parasympathetic activity, impairing cholinergic function and thus contributing to delirium. The elderly are particularly vulnerable to reduced cholinergic transmission, increasing their risk of delirium. Regardless of the cause, the cerebral hemispheres or arousal mechanisms of the thalamus and brainstem reticular activating system become impaired.

Clinical Features

- Delirium may occur at any age but is more common among the elderly. Most cases of delirium occur during hospitalization. When delirium occurs in younger people, it is usually due to drug use or a life-threatening systemic disorder.
- Delirium is characterized primarily by clouding of consciousness, and difficulty maintaining or shifting attention (inattention). Consciousness level fluctuates; patients are disoriented to time and sometimes place or person. There may be illusions, hallucinations and delusions. Speech is often disordered, with prominent slurring, rapidity, neologisms, and aphasic errors.
- Symptoms fluctuate over minutes to hours; they may lessen during the day and worsen at night.
- Patients may become irritable, agitated, hyperactive, and hyperalert, or they may become quiet, withdrawn, and lethargic. Elderly people with delirium tend to become quiet and withdrawn which may be mistaken for depression. Some patients alternate between the two. Other symptoms and signs depend on the cause.

Investigations

- Full blood count, ESR
- Urea, creatinine
- Electrolytes
- Glucose
- Calcium, magnesium
- Liver function tests
- Brain imaging (CT and/or MRI)
- Lumbar puncture
- EEG
- Arterial blood gases
- ECG
- Infection screen (blood cultures, chest X-ray, urine culture).

Management

- Identify and correct the underlying cause.
- Confused patients should be nursed in a well-lit room.
- Maintain adequate hydration and nutrition, treat pain, discomfort, prevent bed sores and minimize the risk of aspiration pneumonitis.
- Low-dose haloperidol (0.5 to 1.0 mg orally, intravenously or intramuscularly) can be used to control agitation or psychotic symptoms.
- Newer antipsychotic agents, quetiapine, risperidone, and olanzapine have similar efficacy to haloperidol with fewer extrapyramidal side effects.
- Benzodiazepines (e.g. lorazepam 0.5 to 1.0 mg) can be used in delirium due to sedative drug and alcohol withdrawal. Benzodiazepines are likely to worsen confusion if used in delirium due to other causes.

Q. Enumerate the causes of intracranial space occupying lesions (mass lesions). Discuss the clinical features, investigations and their management.

Causes of Intracranial Space Occupying Lesions (SOL)

- *Hematomas*: Subdural hematoma, extradural hematoma, intracerebral hematoma.
- *Vascular*: Large aneurysms, hemangiomas.
- *Infective*: Cerebral abscess, tuberculoma (commonest SOL in developing countries), cysticercosis, toxoplasma, echinococcosis (hydatid cysts).
- *Inflammatory*: Sarcoid mass.
- *Neoplastic*: Meningioma, astrocytoma, glioma, ependymoma, medulloblastoma, metastatic brain tumors
- *Others*: Embryonic dysplastic lesions (e.g. craniopharyngiomas, hamartomas), arachnoid cyst, colloid cyst (in the ventricles).

Clinical Features

- Signs and symptoms depend on the site of the leison, its nature and its rate of expansion.
- Frontal lobe lesion causes personality change, urinary incontinence, impaired smell, contralateral hemiparesis and frontal release signs. Non-dominant parietal lobe lesion causes contralateral cortical sensory loss, and hemiparesis. Dominant parietal lobe lesion causes similar signs plus motor aphasia. Temoral lesion causes sensory aphasia (only dominant side), impaired verbal memory, contralateral homonymous upper quadrantanopia, and complex hallucinations (smell, sound, etc.). Occipital lobe lesion causes visual inattention, visual loss, and homonymous hemianopia (with macular sparing).
- Cerebellopontine angle lesions can cause deafness, tinnitus, vertigo and facial palsy.
- Seizures occur in supratentorial lesions.
- Raised intracranial pressure due to lesion causes headache, impairment of conscious level, papilledema, vomiting, bradycardia, and hypertension. Rapidly growing mass lesions are more likely to produce these effects.
- The rise in intracranial pressure may not be uniform and cause displacement of parts of the brain between its various compartments. Temporal lobes herniation through the tentorium due to a large hemisphere mass may cause 'temporal coning' which stretches the 3rd and/or 6th cranial nerves leading to ipsilateral pupilary dilatation and lateral rectus palsy. Pressure on the contralateral cerebral peduncle may cause hemiparesis. Herniation of cerebellar tonsils through the foramen magnum may compress the brainstem and lead to decerebrate posturing and death.

Investigations

- *CT scan*: It shows the site, size, nature and effects of the mass lesion. The nature of the lesion can be made out by CT scan most of the time.
- *Magnetic resonance imaging (MRI)*: More sensitive in picking up early gliomas and posterior fossa leions than CT-scan.
- *CT or MR angiography*: Can pick up anerysms and AV malformations.
- *PET scan*: Can differentiate malignant from benign lesions.
- *Brain biopsy*: Stereotactic brain biopsy is the gold standard to determine the nature of lesions. However, biopsy may not be possible with lesions in certain locations.

Management

General Measures

- Control of raised ICP (mannitol, diuretics).
- Seizure prophylaxis (phenytoin, carbamazepine).

Specific Measures

- Surgical removal of nonmalgnant lesions.
- Surgical removal, chemotherapy and radiotherapy for malignant lesions.
- Appropriate antimicrobial therapy for infective lesions.

Q. Classify brain tumors. What are the clinical features, investigations and management of brain tumors?

Classification of Brain Tumors

Primary Brain Tumors

- These tumors arise in the brain itself. These are further classified as:
  - Gliomas: Astrocytic tumors (astrocytomas, anaplastic astrocytomas, glioblastomas), oligodendroglial tumors, mixed gliomas, ependymal tumors.
  - Medulloblastomas (small, round cell embryonal tumors).
  - Meningiomas.

Secondary Brain Tumors

- These tumours arise somewhere else and involve brain as a metastatic site. These are the most common type of brain tumors.

Clinical Presentation

- Headache (diffuse or localized)
- Seizures

- Nausea and vomiting (due to increased ICT)
- Loss of consciousness (due to sudden raise in ICT which may cut off the brain blood supply)
- Cognitive dysfunction (memory problems and mood or personality change)
- Focal neurological deficits such as motor weakness (UMN type), sensory loss (cortical sensory deficits), aphasia, visual spatial dysfunction, etc. depending on the location of tumor.

Investigations

- CT scan
- MRI scan
- Perfusion MR imaging
- PET scans
- Biopsy of the tumor.

Treatment

- Surgical resection is an option for peripherally situated tumors such as meningioma and acoustic neuroma.
- If there is obstructive hydrocephalus causing significant symptoms surgical shunting procedures help.
- Radiation therapy or combined radiation plus chemotherapy is helpful in malignant gliomas.
- Corticosteroids and mannitol help reduce cerebral edema and are usually started before surgery.
- Anticonvulsants (phenytoin, sodium valproate, carbamazepine, levetiracetam) are prescribed to prevent any seizure attacks.
- Palliative care should be given to those with incurable disease.

Q. Cerebellopontine angle tumors.

Or

Q. Acoustic neuroma.

- Cerebellopontine angle (CP angle) is a shallow triangle lying between the cerebellum, the lateral pons and the petrous bone.

Tumors Found in CP Angle

- Acoustic neuroma (more than 80%) schwannomas)
- Meningioma
- Cholesteatoma
- Hemangioblastoma
- Metastatic tumors
- Potine glioma
- Medulloblastomas
- Astrocytoma
- 5th, 7th, and 9th nerve neuromas
- Lipomas
- Nasopharyngeal carcinoma invasion
- Lymphoma
- Arachnoid cysts
- Aneurysms

Acoustic Neuromas (Vestibular Schwannomas)

- These tumors arise from the Schwann cells of 8th cranial nerve. They account for approximately 80 to 90 percent of CP angle tumors.
- The median age at diagnosis is 50.
- Risk factors for development of acoustic neuroma are loud noise, neurofibromatosis types 1 and 2, and radiofrequency energy due to cell phone (controversial).

Clinical Features of CP Angle Tumors

- Involvement of 7th, 8th, and ophthalmic branch of 5th nerve with or without ipsilateral cerebellar signs is the classical presentation of CP angle tumor.
- Presenting features include ipsilateral hearing loss, tinnitus, vertigo, and unsteadiness (due to 8th nerve involvement.
- Facial numbness and hypesthesia occur due to 5th nerve involvement.
- Facial weakness and taste disturbances occur due to 7th nerve involvement.
- Cerebellar involvement also causes unsteadiness and ataxia.
- Very large tumor can press on the brainstem, obstruct CSF flow and lead to raised ICT and hydrocephalus. Lower cranial nerves (9,10,11,12) can get involved and lead to dysarthria, dysphagia, aspiration, hoarseness and dysarthria.

Investigations

- Contrast CT or MRI scan.
- *Audiometry*: Shows sensorineural hearing loss.

Treatment

- Surgical resection
- Stereotactic radiosurgery—utilizes multiple convergent beams to deliver a high single dose of radiation to a lesion minimizing injury to adjacent structures.
- Stereotactic radiotherapy—utilizes focused doses of radiation given over a series of treatment sessions.
- Proton beam therapy—provides maximal local tumor control with minimal cranial nerve injuries.

Md. Jany baba.

Diseases of Blood

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Q. What are the common presenting symptoms/signs of a hematological disorder?

General Signs and Symptoms

- *Fatigue, malaise, and lassitude are* seen in patients with moderate to severe anemia. Can also be seen in hematologic malignancies.
- *Weight loss is* seen in malignancies, HIV and tuberculosis which can also cause anemia.
- *Fever is* seen in aggressive lymphomas or acute leukemias.

Nervous System Complaints

- *Headache* is seen in severe anemia or polycythemia. Invasion or compression of the brain by leukemia or lymphoma may also cause headache. Hemorrhage into the brain or subarachnoid space in patients with thrombocytopenia or other bleeding disorders may cause sudden, severe headache.
- *Paresthesias* may occur because of peripheral neuropathy in pernicious anemia or secondary to hematologic malignancy or amyloidosis.
- *Confusion* may occur with severe anemia, hypercalcemia (e.g. myeloma), and vit B_{12} deficiency.
- *Impairment of consciousness* may be a result of increased intracranial pressure secondary to hemorrhage or leukemia or lymphoma in the central nervous system.

Eyes

- *Conjunctival plethora* is seen in polycythemia and pallor in anemia.
- *Blindness* may result from retinal hemorrhages secondary to severe anemia and thrombocytopenia.

ENT

- *Vertigo, tinnitus, and "roaring"* in the ears may occur with marked anemia and polycythemia.
- *Epistaxis* may occur in patients with thrombocytopenia and von Willebrand disease.

Oral Cavity

- *Macroglossia* occurs in amyloidosis.
- *Petechiae and Bleeding gums* may occur with bleeding disorders.
- *Gum hypertrophy* due to infiltration of the gingiva with leukemic cells is seen in acute monocytic leukemia (AML).

Lymph Nodes

- *Lymphadenopathy* is seen in lymphoma, blast crisis of CML and CLL.

Chest and Heart

- *Exertional dyspnea and palpitations* are seen in anemia.
- *Congestive heart failure* can cccur in severe anemia.
- *Chest pain* may arise from involvement of the ribs or sternum with lymphoma or multiple myeloma.
- *Tenderness of the sternum* may be seen in chronic myelogenous or acute leukemia.

Gastrointestinal System

- *Dysphagia* may occur due to iron deficeiency (Plummer-Vinson disease).
- *Abdominal fullness, premature satiety, belching,* or *discomfort* may occur because of massive splenomegaly.
- *Abdominal pain* may occur in abdominal crises of sickle cell disease, or acute intermittent porphyria.
- *Gastrointestinal bleeding* related to thrombocytopenia or other bleeding disorder may be occult but often is manifest as *hematemesis* or *melena.*

Genitourinary and Reproductive Systems

- *Priapism* (painful penile erection) may occur in leukemia or sickle cell disease.
- *Hematuria* may be a manifestation of hemophilia A or B. *Red urine* may also occur with intravascular hemolysis (hemoglobinuria), myoglobinuria, or porphyrinuria.
- *Menorrhagia* is seen in thrombocytopenia and other bleeding disorders.

Musculoskeletal System

- *Back pain* is seen in hemolytic transfusion reactions, involvement of bone or the nervous system in acute leukemia or lymphoma and myeloma.
- *Arthritis* or *arthralgia* may occur with gout secondary to increased uric acid production
- *Bone pain* may occur with bone involvement by the hematologic malignancies, sickle cell anemia, and myelofibrosis. In patients with Hodgkin lymphoma, ingestion of alcohol may induce pain at the site of any lesion, including those in bone.
- *Muscle and joint hematomas* are seen in hemophilia.

Skin and Nails

- *Pallor* is seen in anemia.
- *Platynychia* (flat nails) and *koilonychia* (spoon shaped nails) are seen in iron deficiency anemia.
- *Jaundice* may be present in pernicious anemia or hemolytic anemia. Jaundice may also occur in patients with hematologic malignancies as a result of liver involvement or biliary tract obstruction.
- *Cyanosis* occurs with methemoglobinemia, sulfhemoglobinemia and polycythemia.
- *Itching* may occur in Hodgkin lymphoma and polycythemia vera.
- *Petechiae* and *ecchymoses* are seen in patients with thrombocytopenia, platelet function abnormalities and von Willebrand disease.
- *Infiltrative lesions* may occur in the leukemias (leukemia cutis) and lymphomas (lymphoma cutis) and are sometimes the presenting complaint.
- *Leg ulcers* are common in sickle cell anemia.

Q. What are the common laboratory abnormalities of hematological diseases?

- Anemia (low Hb)
- Polycythemia (high Hb)
- Leucopenia (low white cell count)
- Leucocytosis (high white cell count)
- Thrombocytopenia (low platelet count)
- Thrombocytosis (high platelet count)
- Pancytopenia (all three blood cells low)
- Abnormal coagulation parameters.

Q. Describe the various abnormalities that can be seen in peripheral blood smear.

Q. Importance of blood smear examination.

- Examination of the peripheral blood smear is an inexpensive but powerful diagnostic tool. It provides important clues in the diagnosis of anemias and various disorders of leukocytes and platelets.

RBC Abnormalities

Microcytosis

- Reduced RBC size, MCV < 76 fl.
- Seen in iron deficiency, thalassemia and sideroblastic anemia.

Macrocytosis

- Increased RBC size, MCV > 100 fl.
- Seen in vitamin B_{12}/folate deficiency, liver disease, alcohol intake, hypothyroidism and drugs (e.g. zidovudine).

Target Cells

- Central area of hemoglobinisation, surrounded by a ring of pallor and an outer area of hemoglobin.
- Seen in liver disease, thalassemia, post-splenectomy and hemoglobin C disease.

Spherocytes

- These are spherical shaped RBCs with no area of central pallor.
- Seen in hereditary spherocytosis, autoimmune hemolysis, and postsplenectomy.

Fragmented RBCs (Schistocytes, Helmet Cells)

- These are seen in disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP).

Nucleated Red Blood Cells (Normoblasts)

- These are immature RBCs prematurely released into the circulation.
- Seen in marrow infiltration, severe hemolysis, myelofibrosis and acute hemorrhage.

Howell-Jolly Bodies

- These are small round nuclear remnants which are normally removed by the spleen.
- Seen in hyposplenism and post-splenectomy.

Heinz Bodies

- Heinz bodies are aggregates of denatured hemoglobin and are not normally found red cells.
- They are found in glucose-6-phosphate dehydrogenase deficiency and thalassemias.
- Heinz bodies are not visible on routine staining, but become visible on a supravital dye such as crystal violet.

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Polychromasia

- This refers to the presence of young RBCs and reticulocytes which are prematurely released into the circulation.
- Seen in haemolysis, acute hemorrhage, and increased red cell turnover.

Basophilic Stippling

- This refers to the presence of blue granules in the cytoplasm of RBCs, which represent ribosomal precipitates.
- They are most often seen in the thalassemias, alcohol abuse, lead and heavy metal poisoning, and the rare condition hereditary pyrimidine 5′-nucleotidase deficiency.

WBC Abnormalities

- Cytoplasmic vacuolization of granulocytes is seen in patients with bacteremia or other severe infections. Toxic granulation is found in infections and metabolic derangements.
- Hypersegmented neutrophils are seen in vitamin B_{12} or folic acid deficiency
- A high percentage of reactive lymphocytes may be seen in viral illnesses such as infectious mononucleosis, viral hepatitis, cytomegalovirus infection, HIV infection, etc.
- Blasts, which are immature cells with large nuclei, nucleoli, and a scant rim of dark blue cytoplasm are found in leukemias.
- Cells with Auer rods (a rod-like conglomeration of granules in the cytoplasm) within a blast cell are pathognomonic of acute myelogenous leukemia (AML).
- Small lymphoid cells with cleaved nuclei may be seen in patients with follicular lymphoma.
- Lymphoid cells with "hairy" cytoplasm may be seen in hairy cell leukemia.
- Lymphoid cells with hyperlobulated nuclei may be seen in patients with adult T cell leukemia/lymphoma.
- Atypical lymphoid cells with "cerebriform" nuclei (Sezary cells) may be seen in patients with cutaneous T cell lymphoma.

Platelet Abnormalities

- Giant platelets are seen in ITP, disseminated intravascular coagulation, myeloproliferative disorders, and megaloblastic anemias. Microthrombocytes are found in the Wiskott-Aldrich syndrome.

Q. Define anemia.

Q. Give the causes and classification of anemia.

- Anemia is defined as a reduction in the number of circulating RBCs.

Anemia can be classifeied based on the underlying cause or morphology of RBCs (Table 6.1).

Table 6.1 Classification of anemia

I. Based on underlying process

Decreased RBC production
- Iron, B_{12}, or folate deficiency
- Bone marrow disorders (e.g. aplastic anemia, pure RBC aplasia, myelodysplasia, tumor infiltration)
- Bone marrow suppression (e.g. drugs, chemotherapy, irradiation)
- Low levels of trophic hormones which stimulate RBC production, such as erythropoietin (e.g. chronic renal failure), thyroid hormone (e.g. hypothyroidism), and androgens (e.g. hypogonadism)
- Anemia of chronic disease/inflammation

Increased RBC destruction
- Inherited hemolytic anemias (e.g. hereditary spherocytosis, sickle cell disease, thalassemia major, PNH)
- Acquired hemolytic anemias (e.g. Coombs'-positive autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, malaria, hypersplenism)

Blood loss
- Acute blood loss (e.g. trauma, hematemesis, hemoptysis)
- Chronic blood loss (e.g. slowly bleeding ulcer or carcinoma)
- Induced bleeding (e.g. repeated diagnostic testing, hemodialysis losses, excessive blood donation)

II. Based on the morphology of RBC

Microcytic anemia (MCV below 80 fl)
- Iron deficiency
- Anemia of chronic disease
- Thalassemia
- Copper, vit C, and pyridoxine deficiency

Macrocytic anemia (MCV above 100 fl)
- Vit B_{12} and folate deficiency
- Drugs interfering with nucleic acid synthesis (zidovudine and hydroxyurea)
- Abnormal RBC maturation (e.g. myelodysplastic syndrome, acute leukemia, LGL leukemia, alcohol abuse, liver disease, and hypothyroidism)

Normocytic anemia (MCV normal, i.e. between 80 and 100 fl)
- Acute blood loss

Q. Iron metabolism in the body.

- Iron is vital for all living organisms because it is essential for multiple metabolic processes, including oxygen transport, DNA synthesis, and electron transport. Iron (Fe) is an important component of hemoglobin, myoglobin, and many enzymes in the body.

Normal Iron Requirements

- Daily requirement of iron ranges from 1 to 3 mg, and is more during periods of growth, menstruation, pregnancy and lactation.

Iron Intake and Absorption

- Red meat, liver, egg yolk, blood and bone marrow are rich sources of iron. For a vegetarian, sources of iron are green leafy vegetables, dry fruits and jaggery. Milk is a poor source of iron (0.8 mg/L). Iron is present in the outer layers of cereals and hence, polished rice contains less iron than unpolished rice. Cooking utensils of iron may contribute to the iron content of food.
- Non-vegetarian diets contain haem iron which is absorbed better because it is not affected by various intraluminal factors which affect the bioavailability of iron. Iron in egg is complexed with phosphates and is poorly absorbed. In vegetarian food, iron is in the ferric form and is converted into ferrous form before absorption.
- Gastric acid and ascorbic acid (vit C) help in this process by maintaining iron in reduced and soluble form. Phytates, phosphates and oxalates interfere with iron absorption by forming insoluble complexes with iron.
- Iron absorption mainly occurs in duodenum. Two steps are involved in the absorption of iron: entry of iron from the intestinal lumen into the mucosal cell, and its passage from the mucosal cell into the plasma. Iron absorption is increased with decreased iron stores and during pregnancy. Plasma iron is bound to transferrin.

Distribution of Iron in the Body

- An average adult male has about 4 g and an adult female about 3 g of iron in the body. 70% of this is in the form of hemoglobin. Iron is stored in the cells of the reticulo-endothelial system mainly in the liver, spleen and bone marrow.
- Storage iron is in two forms: ferritin and hemosiderin. Iron in ferritin is in the form of ferric hydroxyphosphate and in hemosiderin in the form of ferric oxide.
- When hemoglobin formation exceeds its destruction, iron is mobilized from the stores, whereas when hemoglobin production is less than the destruction or when iron is absorbed in excess of requirement, iron is deposited in the stores.

Iron Excretion

- Iron is lost by desquamation of epithelium of gut, genito-urinary tract and the skin. An adult male loses 1 mg of iron daily this way. A menstruating female loses about 2 mg of iron daily. A small amount of iron is lost in the milk during lactation.

Q. Enumerate the causes of microcytic anemia. Discuss the etiology, clinical features, investigations and management of iron deficiency anemia.

Q. Pica.

Q. Plummer-Vinson syndrome (Paterson-Kelly syndrome).

Q. Oral iron therapy.

Q. Parenteral iron therapy.

Causes of Microcytic Anemia (MCV below 80 fl)

- Iron deficiency
- Anemia of chronic disease
- Sideroblastic anemia
- Thalassemias
- Copper, vit C, and pyridoxine deficiency

Iron-deficiency Anemia

- Iron deficiency is the most common cuase of microcytic anemia. Other than hemoglobin, iron is also a part of many enzymes in the body which are vital for tissue respiration and organ function.
- Iron is the commonest deficiency disease all over the world. It is widely prevalent in India and is more common in pregnant women.

Causes of Iron Deficiency

Decreased iron intake or absorption
- Inadequate diet
- Malabsorption (celiac sprue, Crohn's disease, post-gastrectomy)
- Acute or chronic inflammation

Increased demand for iron
- Rapid growth in infancy or adolescence
- Pregnancy
- Erythropoietin therapy

Increased iron loss
- Acute blood loss (blood donation, trauma)
- Chronic blood loss (peptic ulcer, GI malignancy, hook worm infestation, menses)

Clinical Features

- Clinical features include those due to anemia and those due to underlying disease causing iron deficiency.

Symptoms

- Insidious onset of weakness, dyspnea, effort intolerance and easy fatigability.

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- Palpitations, tinnitus and headache due to hyperdynamic circulation.
- Dysphagia which is more for solids than for liquids due to formation of mucosal webs at the pharyngo-esophageal junction (Plummer-Vinson syndrome).
- Amenorrhea or menorrhagia, excess hair loss and Pica due to iron deficiency.
- Geophagia is common in children and pregnant women. Pagophagia (excessive eating of ice) may be seen, especially in women. All forms of pica are relieved by iron therapy even before the anemia is corrected.
- Iron deficiency also causes functional impairment of various tissues such as the myocardium, peripheral nerves, jejunum, cerebral cortex, kidneys and liver.

Signs

- Glossitis and angular stomatitis may be present. Papillary atrophy of the tongue makes it appear smooth and pale (bald tongue).
- Flattening and concavity of the nails are called platynychia and koilonychia respectively, and are seen earlier in toe nails than in finger nails.
- Mild hepatosplenomegaly may be present.
- The triad of dysphagia due to esophageal webs, koilonychia and splenomegaly in a patient with iron deficiency anemia is known as the *Plummer-Vinson* or *Paterson-Kelly syndrome*. Webs and dysphagia do not respond to iron therapy. Dysphagia is treated by passage of bougei and dilatation. These webs are premalignant.

Investigations

- Investigations are required to confirm the diagnosis of iron deficiency and to determine its cause.
- Complete blood picture—RBC count, hemoglobin, hematocrit, MCV, MCH and MCHC are all decreased in iron deficiency anemia.
- Peripheral blood smear shows microcytic hypochromic RBCs. There may be other morphological abnormalities such as poikilocytosis and presence of target cells. Reticulocyte count is normal unless the patient had a recent acute blood loss, or has received hematinics.
- Serum iron is decreased, TIBC is increased, and transferrin saturation is less than 16%. Serum ferritin is less than 10 μg/L.
- Bone marrow shows micronormoblasts. Iron stores are absent or markedly reduced.
- Investigations to identify the cause of iron deficiency—stool for occult blood and helminthiasis, upper GI scopy to rule out peptic ulcer or malignancy, etc. depending on the clinical presentation.

Treatment

- Treatment involves replacement of iron and correction of the cause of iron deficiency. Iron can be given orally or parenterally.

Oral Iron Therapy

- Oral iron therapy is safer and cheaper than parenteral, and is preferred.
- Iron is best given as a single dose at bedtime.
- There are many iron salts available such as ferrous fumarate, ferrous sulfate and ferrous gluconate. There is no significant difference in the absorption of these salts. Oral iron is better tolerated if given after food, but may be absorbed less efficiently.
- Iron is better absorbed in the ferrous form than in the ferric. Iron absorption is increased by simultaneous administration of ascorbic acid and decreased by antacids, certain antibiotics (e.g. quinolones, tetracycline), dietary fiber, tea, coffee, eggs, or milk.
- Hemoglobin level will normalize in about 6–8 weeks of iron therapy. However, iron therapy has to be continued for a total of 6 months to ensure repletion of the body iron stores.
- Adverse effects of oral iron include nausea, vomiting, epigastric discomfort, constipation or diarrhea. They are dose-related, and can be reduced by gradually increasing the dose and giving it after meals.

Parenteral Iron Therapy

- *Indications*: It is indicated in patients who cannot tolerate oral iron and in pregnant women who present with severe anemia very late in pregnancy. Patients with gastro-intestinal diseases such as peptic ulcer and ulcerative colitis are likely to be aggravated by oral iron and need parenteral iron.
- *Parenteral preparations*: There are many parenteral iron preparations available. These are iron dextran (can be given either IM or IV), ferric gluconate complex and iron sucrose (only for IV use). Injection should be given after a test dose because there is a small risk of anaphylaxis. Intramuscular iron should be given by the 'Z' track technique to prevent staining of the skin at the injection site.
- Iron can be given as single dose IV infusion. For giving total dose iron therapy, the dose of iron can be calculated by the formula $[(2.38 \times W \times D) + 1000]$, where W is body weight in kg and D is the hemoglobin deficit in g/dl (15 – patient's hemoglobin). The value obtained is the required quantity of iron in mg. The addition of 1000 mg is provision for the body iron stores.

- *Side effects*: Both local and systemic side effects can occur following use of iron dextran. Local reactions include pain, muscle necrosis, and phlebitis in adjacent vessels. Anaphylactic reactions also can occur with all the preparations but less with ferric gluconate complex and iron sucrose than iron dextran. Other systemic effects include fever, urticaria, joint pains, nausea, vomiting, diarrhea, abdominal pain, backache, bodyache, chest pain, angioneurotic oedema, and hypotension.

Treatment of Cause of Iron Deficiency

- For example, treatment of hookworm infestation, piles, peptic ulcer disease and any other bleeding lesions.

Q. Enumerate the causes of macrocytosis.

Abnormal nucleic acid metabolism of erythroid precursors
- Vitamin B_{12} (cobalamin) deficiency
- Folate deficiency
- Drugs (hydroxyurea, zidovudine, methotrexate, azathioprine)

Abnormal RBC maturation
- Myelodysplastic syndrome
- Acute leukemia
- LGL leukemia
- Multiple myeloma and other plasma cell disorders

Conditions causing reticulocytosis
- Erythropoietin therapy
- Acute blood loss

Others
- Alcohol abuse
- Liver disease
- Hypothyroidism
- Hyperlipidemia

Q. Enumerate the causes of macrocytic anemia. Discuss the etiology, clinical features, diagnosis and management of vit B_{12} (cyanocobalamin) deficiency.

Q. Bone marrow picture in megaloblastic anemia.

- RBCs with MCV more than 100 fl (femtoliters) are called macrocytes (megaloblasts).

Causes of Macrocytic Anemia

- Vitamin B_{12} deficiency
- Folic acid deficiency
- *Drugs*: 6-mercaptopurine, azathioprine, 5-fluorouracil, hydroxyurea, acyclovir, zidovudine
- Hereditary orotic aciduria
- Lesch-Nyhan syndrome
- Congenital dyserythropoietic anemia

Vitamin B_{12}

- Vitamin B_{12} is found in animal proteins and dairy products. Vegetables contain practically no B_{12}. Vegetarians get their B_{12} by dairy products.
- Normal recommended dietary allowance for vit B_{12} is 2 µg/day. Total body stores of vit B_{12} is 2 to 5 mg, half of which is in the liver. These stores are enough for approximately 3 years, and hence, it takes approximately 3 years to develop manifestations of vit B_{12} deficiency after absorption of dietary B_{12} ceases.
- Dietary B_{12} is liberated in the stomach in the presence of acid and pepsin in the stomach and binds to gastric-derived intrinsic factor (IF). IF is a glycoprotein with very high affinity for B_{12}. The IF-B_{12} complex binds to a

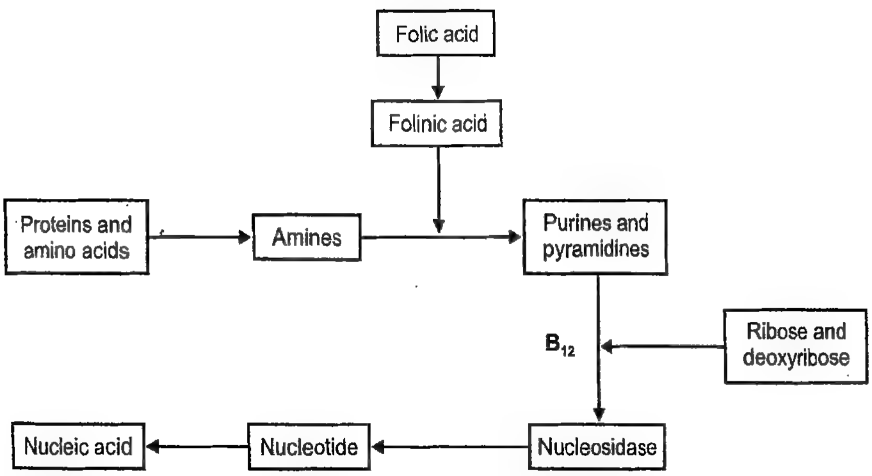

Fig. 6.1: Role of vitamin B_{12} and folic acid in the synthesis of nucleic acid

specific receptor in the ileum, and is absorbed by an active process. In the plasma B_{12}, is bound to a protein called transcobalamin.

Physiological Role of Vitamin B_{12}

- Vitamin B_{12} is very important for nucleic acid synthesis in every cell. Actively growing and dividing cells, which synthesise DNA rapidly, e.g. mucosal cells and hemopoietic cells, are likely to be particularly affected in B_{12} deficiency. It is also important for the normal integrity of nervous system.
- Thymine (a purine) is important for DNA synthesis. Synthesis of thymine requires tetrahydrofolate (THF). Vitamin B_{12} is required for conversion of methyl THF to THF. Thus lack of vitamin B_{12} causes impaired DNA synthesis and cell division. RNA synthesis continues, resulting in a large cell with a large nucleus. All cell lines have dyspoiesis, in which cytoplasmic maturity is greater than nuclear maturity; this dyspoiesis produces megaloblasts in the marrow before they appear in the peripheral blood. Dyspoiesis results in intramedullary cell death (intramedullary hemolysis), making erythropoiesis ineffective and causing indirect hyperbilirubinemia and hyperuricemia. Because dyspoiesis affects all cell lines, pancytopenia develops in advanced stages of vit B_{12} deficiency. Hypersegmentation of neutrophils is common, the mechanism of which is unknown.

Etiology of Vitamin B_{12} Deficiency

Inadequate intake
- Strict vegetarians

Intrinsic factor deficiency
- Pernicious anemia
- Gastrectomy
- Atrophic gastritis

Decreased absorption
- Malabsorption syndromes
- Ileal resection or bypass
- Crohn's disease
- Blind loops
- Fish tapeworm infestation
- Pancreatitis

Agents that block absorption
- Neomycin
- Biguanides (e.g. metformin)
- Proton pump inhibitors (e.g. omeprazole)

Clinical Features

- Symptoms related to anemia such as easy fatigability, weakness, dyspnea, and effort intolerance.
- Hyperdynamic circulation due to anemia may lead to palpitations, tinnitus and headache.
- Vit B_{12} deficiency causes atrophic glossitis and neurologic symptoms.
- Vit B_{12} deficiency causes symmetrical peripheral neuropathy (with paresthesias, ataxia, loss of vibration and position sense). In severe deficiency, subacute combined degeneration (SCD) of the spinal cord may develop. In SCD, there is involvement of posterior columns and corticospinal tract. Manifestations of SCD are paresthesias, ataxia, loss of vibration and position sense due to posterior column involvement and weakness, spasticity, clonus, and paraplegia due to corticospinal tract involvement.
- Other neurologic symptoms of vit B_{12} deficiency include memory loss, irritability, and dementia.

Investigations

Complete Blood Count

- Hemoglobin level is low.
- Mean corpuscular volume (MCV) is over 100 fl (normal 80–95).
- Mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are usually normal.

Peripheral Smear

- Shows oval macrocytes, few myelocytes and occasional normoblasts. There is anisocytosis and poikilocytosis. Reticulocyte count is low in relation to degree of anemia. Hypersegmented neutrophils are common. When the anemia is severe, there may be leucopenia and thrombocytopenia (pancytopenia) and megaloblasts may be seen in the peripheral blood smear.

Bone Marrow

- Bone marrow is hypercellular with frequent mitoses and increased myeloid—erythroid ratio. There is abundant iron store. The characteristic features are: Presence of megaloblasts, giant bands and giant metamyelocytes.
- Megakaryocytes are decreased with basophilic agranular cytoplasm and hypersegmented nucleus.

Vit B_{12} and Folic Acid Levels

- The normal vit B_{12} level is 300 to 900 pg/ml; values <200 pg/ml indicate clinically significant deficiency. Serum homocysteine and methylmalonic acid levels are high in vit B_{12} deficiency.

Other Tests

- Schilling test can be done to diagnose the cause of vit B_{12} deficiency.

- Upper GI scopy is useful in cases of pernicious anemia.
- Jejunal biopsy is useful in malabsorption disorders.

Treatment

General Management

- This is similar to other cases of anemia. For severe symptomatic anemia (Hb <7 g/dl), packed red cell transfusion is given. Before transfusion it is necessary to collect samples for B_{12} and folic acid estimation.

Vit B_{12} Replacement

- Vit B_{12} should be replaced by parenteral route since malabsorption is the cause most of the time. 1000 μg should be given intramuscularly per week for 8 weeks, followed by 1000 μg every month for the rest of the patient's life.
- Oral replacement therapy with 2 mg vit B_{12} per day is also effective if malabsorption is not the cause of deficiency.
- Patient will experience increase in strength and well-being even before hematological response. Marrow morphology begins to revert toward normal within a few hours after treatment is initiated. Reticulocytosis begins 4 to 5 days after therapy is started and peaks at about day 7, with subsequent remission of the anemia over the next several weeks.
- Any underlying cause of vit B_{12} deficiency should be treated (e.g. antibiotics for intestinal bacterial overgrowth, deworming for tapeworm infestation).

Q. Pernicious anemia.

- Pernicious anemia is due to B_{12} deficiency caused by the absence of intrinsic factor, due to either atrophy of the gastric mucosa or autoimmune destruction of parietal cells. The disease was given its common name because it was fatal (pernicious) prior to the discovery of treatment, similar to leukemia at that time.
- It is common in whites, and rare in Asians. Females are affected more often than males. It is a disease of the elderly, the average patient presenting near age 60; it is rare under age 30. Patients are likely to be having blood group A.

Pathogenesis

- Intrinsic factor is important for the absorption of B_{12}. Intrinsic factor deficiency causes less absorption of B_{12} and its deficiency. Gastric atrophy also results in hypochlorhydria and malabsorption of B_{12}.
- Pernicious anemia may be associated with other autoimmune diseases such as thyroid disorders, Addison's disease, hypoparathyroidism, diabetes mellitus, and rheumatoid arthritis.
- Ninety percent of patients have parietal cell antibody in serum and 50% have antibody to intrinsic factor which inhibits binding of B_{12} to intrinsic factor.

Clinical Features

- Clinical features are similar to B_{12} deficiency anemia.

Investigations

- In addition to tests done for vitamin B_{12} deficiency, antibodies to parietal cell and antibodies to intrinsic factor may be demonstrated in serum and gastric juice. Serum gastrin levels are elevated.
- *Histamine or pentagastrin test*: Acid secretion does not increase even after injection of histamine or pentagastrin.
- *Barium meal examination*: This shows atrophic mucosal pattern of stomach.
- *Upper GI scopy and mucosal biopsy*: These show atrophic gastritis.

Treatment

- Treatment is similar to B_{12} deficiency anemia.

Q. Schilling test (vit B_{12} absorption test)

- This test is performed to determine the cause for vitamin B_{12} malabsorption. Vitamin B_{12} is absorbed in the terminal ileum.
- Causes of vitamin B_{12} malabsorption are intrinsic factor defficiency, atrophic gastritis, small intestinal bacterial overgrowth, exocrine pancreatic insufficiency, and ileal disease.
- Schilling test is performed by administering 1 mcg of radiolabelled vit B_{12} orally, followed by an intramuscular injection of 1000 μg of vit B_{12} one hour later to saturate vit B_{12} binding sites so that absorbed radiolabelled B_{12} is excreted in the urine.
- A 24-hour urine is then collected for determination of the percent excretion of the oral dose. Normally at least 10% of the radiolabeled vitamin B_{12} is excreted in the urine. In patients with pernicious anemia or with deficiency due to impaired absorption, less than 10% of the radiolabeled vitamin B_{12} is excreted.
- Next, the above step is repeated after the addition of intrinsic factor. If this second urine collection is normal, it proves intrinsic factor deficiency or pernicious anemia.
- If urinary excretion of vit B_{12} is still less than 10% after adding intrinsic factor, then the test is repeated after a course of antibiotics. Small intestinal bacterial overgrowth is suggested if an abnormal test is normalized

after a course of antibiotics. If the absorption is abnormal even after addition of intrinsic factor and exclusion of bacterial overgrowth, it suggests terminal ileal disease. The Schilling test can also be abnormal in pancreatic insufficiency and celiac disease. Normalization after pancreatic enzyme substitution or a gluten-free diet is useful for diagnosis of these causes of malabsorption.

- The Schilling test can also be used to determine the functional integrity of the ileal mucosa after treatment of ileal Crohn's disease.
- Many labs have stopped doing the Schilling test, due to lack of production of radiolabeled-B_{12} test substances. Also, the treatment remains same (i.e. injection of vit B_{12}), even if the exact cause were identified. Hence, it is not being performed now.

Q. Discuss the etiology, clinical features, diagnosis and management of anemia due to folic acid deficiency.

Sources of Folic Acid

- Folic acid (folate) occurs in animal products and green leafy vegetables in the polyglutamate form. High amounts are present in liver, kidney, spinach, cabbage, yeast, nuts and fruits. Milk and eggs are poor in folate. It is easily destroyed by cooking.

Metabolism

- Polyglutamates in food are cleaved to monoglutamate in the jejunum where it is absorbed. Folates enter plasma and are taken up by liver and other cells.
- Folate is mainly stored in liver. These stores are enough for approximately 3 months and hence, manifestations of deficiency appear after 3 months of deficient diet.

Physiological Role

- Folate is very important for nucleic acid synthesis in every cell. Actively growing and dividing cells, which synthesize DNA rapidly, e.g. mucosal cells and hemopoietic cells, are likely to be particularly affected in folate deficiency.
- Normal daily folate requirement for adults is 1 to 2 mg / day.

Causes of Folic Acid Deficiency

Inadequate intake
- Alcoholics
- Poor dietary intake
- Overcooked foods

Increased requirements
- Pregnancy
- Infancy
- Malignancy
- Increased hematopoiesis (chronic hemolytic anemias)
- Exfoliative skin disorders

Malabsorption
- Tropical and nontropical sprue
- Inflammatory bowel disease
- Short bowel syndrome

Drugs
- Methotrexate
- Trimethoprim
- Pyrimethamine
- Phenytoin

Clinical Features

- Macrocytic anemia.
- Folate deficiency does not cause neurologic symptoms (unlike vit B_{12} deficiency). Only depression, irritability, poor judgement, forgetfulness and sleep deprivation have been seen in some patients.
- Glossitis is less common than in vitamin B_{12} deficiency.
- Anorexia and occasional diarrhea may be present.

Investigations

- Low serum folate levels (normal—6 to 20 ng/ml; values ≤4 ng/ml are diagnostic of folate deficiency).
- Peripheral blood smear shows macrocytes.
- Bone marrow shows megaloblastic picture.
- Elevated serum homocystiene levels and normal methylmalonic acid levels.

Management

- Correct the underlying cause.
- Oral folic acid supplementation (5–15 mg/day) should be given in deficiency states.
- It should be given prophylactically (350 μg/day) to all pregnant women, premature babies, patients receiving dialysis, and in severe and chronic hemolytic states.
- Patients receiving folic acid antagonists such as methotrexate should be given folinic acid daily orally (15 mg).
- In the presence of vit B_{12} deficiency, folate therapy can aggravate neurological symptoms. Hence, care should be taken to replace vit B_{12} before folate therapy.

Q. What are the causes of blood loss anemia? How do you manage it?

Causes of Blood Loss Anemia

Acute blood loss
- Trauma
- Hematemesis
- Hemoptysis
- Rupture of ectopic pregnancy

Chronic blood loss
- Slowly bleeding peptic ulcer
- GI malignancy
- Hookworm infestation

Induced bleeding
- Repeated diagnostic testing
- Hemodialysis losses
- Excessive blood donation

Clinical Features

- Anemia due to acute blood loss is symptomatic if severe. Losses of up to 20% of the blood volume can be asymptomatic. Blood loss more than this can cause anxiety, hypotension, syncope, tachycardia, breathlessness, and shock. Hemoglobin level immediately after the bleed may be normal as it takes some time for hemodilution to occur.
- Chronic blood loss as happens in hookworm infestation, peptic ulcer, etc. can produce severe anemia which can be asymptomatic. Symptoms will not appear until severe anemia develops.

Treatment

- In acute blood loss, volume replacement either by blood transfusion, or IV fluids is very important.
- In chronic blood loss anemia, if the patient is severely anemic, packed RBC should be transfused.
- Underlying cause of blood loss should be treated in both acute and chronic blood loss.

Q. Anemia of chronic disease.

- The anemia of chronic disease (ACD), also termed the anemia of chronic inflammation, is associated with many chronic diseases (infectious, inflammatory, neoplastic disease, severe trauma, heart disease, diabetes mellitus, etc). Though ACD occurs in chronic diseases, it can begin acutely during virtually any infection or inflammation.

Pathophysiology

- Three pathophysiologic mechanisms have been identified in ACD: (1) Shortened RBC survival due to unknown mechanisms, (2) Impaired erythropoiesis due to decreases in both erythropoietin (EPO) production and marrow responsiveness to EPO and (3) Impaired intracellular iron metabolism.
- Reticuloendothelial cells retain iron from senescent RBCs, making iron unavailable for Hb synthesis. There is thus a failure to compensate for the anemia with increased RBC production. Macrophage-derived cytokines (e.g. IL-1, TNF, interferon) contribute to the decrease in EPO production and the impaired iron metabolism.

Clinical Features

- Most patients have mild anemia that produces no symptoms. Signs and symptoms of underlying disease may be present.

Investigations

- The anemia is normocytic-normochromic and rarely microcytic-hypochromic.
- Reticulocyte count, leucocyte count and platelet counts are normal.
- The serum iron concentration and transferrin level (also measured as total iron binding capacity, TIBC) are both low and the percent saturation of transferrin is usually normal, which should distinguish ACD from iron deficiency anemia, in which transferrin saturation is low.

Treatment

- Correction of the underlying disorder.
- Iron supplements.
- Administration of recombinant human erythropoietin if anemia is severe.

Q. Discuss the classification, clinical features, diagnosis and management of hemolytic anemias.

- Anemia resulting from increased red cells destruction is called hemolytic anemia. Hemolysis can be defined as a shortening of RBC survival to less than 100 days (normal 120 days).
- Normal marrow has tremendous capacity to compensate for hemolysis, hence anemia occurs only when compensation is not adequate.
- Hemolysis may be an extravascular or an intravascular phenomenon. Autoimmune hemolytic anemia (AIHA) and hereditary spherocytosis are examples of extravascular hemolysis because the red blood cells are destroyed in the spleen and other reticuloendothelial tissues. Others are due to intravascular hemolysis.

Classification of Hemolytic Anemias

Hereditary

- *Membrane defects*: Spherocytosis, elliptocytosis and spur cell anemia
- *Enzyme defects*: G6PD deficiency and pyruvate kinase deficiency
- *Hemoglobin defects*: Thalassaemias and sickle cell anemia

Acquired

- Paroxysmal nocturnal hemoglobinuria (PNH)
- *Immune mediated*: Autoimmune hemolytic anemia, incompatible blood transfusion
- *Mechanical*: Prosthetic heart valves and march hemoglobinuria
- *Drugs*: Dapsone and primaquine
- *Infections*: Malaria

Clinical Features

History

- Patient may complain of fatigue and other symptoms of anemia.
- Mild jaundice (lemon yellow).
- H/o passing red-brown urine (due to hemoglobinuria).
- Left hypochondrial pain due to splenomegaly.
- Right hypochondrial pain due to cholelithiasis. Pigment stones occue due to increased production of bilirubin from hemolysis.
- Family history may be present.
- Drug history may be positive.
- Symptoms of any underlying disease responsible for hemolysis.

Physical Findings

- Anemia.
- Mild jaundice.
- Splenomegaly.
- Hemolytic facies due to marrow hyperplasia in skull bones and other bones.
- Ankle ulcers (seen in sickle cell anemia).
- Signs of any underlying disease responsible for hemolysis.

Investigations

Evidence of Increased RBC Destruction

- Indirect hyperbilirubinemia, usually less than 5 mg/dl.
- Increased urobilinogen excretion in urine.
- Decreased plasma haptoglobin and hemopexin.
- Increased plasma lactate dehydrogenase (LDH).
- Shortened RBC survival as demonstrated by chromium-51-labelled RBCs.

Evidence of Increased RBC Production

- Increased reticulocyte count (reticulocytosis).
- Finding premature RBCs in peripheral smear (macrocytes, polychromasia, nucleated RBCs).
- Erytroid hyperplasia of bone marrow.

Additional Findings in Intravascular Hemolysis

- Hemoglobinuria.
- Hemosiderinuria.

Tests to Diagnose Underlying Cause of Hemolysis

- Peripheral blood smear examination.
- Coombs' test (to detect antibodies causing hemolysis).
- Hemoglobin electrophoresis (for thalassemias).
- Osmotic fragility, sucrose lysis and hams test (for membrane defects).
- Measurement of enzyme activity (G6PD, pyruvate kinase).
- Other tests are done depending on the suspected underlying cause.

Treatment

Supportive Therapy

- Blood transfusion for severe anemia
- Replacement of vitamins due to increased erythropoiesis (iron, folic acid)
- Treatment of infections
- Treatment of ankle ulcers
- Splenectomy in selected cases

Specific Therapy

- This depends on the underlying cause—steroids for immune hemolytic anemia, splenectomy in sickle cell anemia and hereditary spherocytosis, withdrawal of offending drug, etc.

Q. Classify immune hemolytic anemias. Discuss the clinical features, diagnosis and management of warm antibody autoimmune hemolytic anemia (AIHA).

- Hemolysis secondary to antibodies against red cell antigens is called immune hemolysis.
- It can be broadly divided into autoimmune and alloimmune hemolytic anemias. In autoimmune hemolytic anemia, antibodies are directed against persons own RBCs. In alloimmune hemolytic anemia, antibodies are directed against transfused RBCs.

Etiology and Classification of Immune Hemolytic Anemias

Autoimmune hemolytic anemia (AIHA)

Warm-antibody AIHA
- Idiopathic
- Chronic lymphocytic leukemia
- Hodgkin's lymphoma
- Systemic lupus erythematosus
- Drugs

Cold agglutinin syndrome
- Idiopathic
- *Mycoplasma pneumoniae*
- Infectious mononucleosis
- Virus infection

Paroxysmal cold hemoglobinuria (PCH)
- Idiopathic
- Viral infections
- Syphilis

Atypical AIHA
- Antiglobulin test-negative AIHA
- Combined cold and warm AIHA (biphasic)

Allo-immune hemolytic anemia
- Hemolytic transfusion reactions
- Hemolytic disease of newborn

Warm Antibody Autoimmune Hemolysis

- Here the antibodies react with RBC antigens at body temperature, hence called warm antibody autoimmune hemolysis. Hemolysis occurs primarily in the spleen. Antibodies are of IgG type.
- The disease is common in adults above the age of 40 years; more common in females.

Etiology

- Many conditions can induce warm antibody formation, which are as follows:
  - Idiopathic (commonest cause)
  - Connective tissue diseases (e.g. systemic lupus erythematosus)
  - Malignancies of the immune system (non-Hodgkin's lymphoma, chronic lymphocytic leukemia)
  - Previous blood transfusion or hematopoietic cell transplantation
  - Drugs (alpha-methyldopa, sulfonamides, NSAIDs, methotrexate)

Clinical Features

- Onset is insidious.
- Symptoms of anemia—fatigue, palpitations.
- Symptoms of hemolysis—mild jaundice, dark urine.
- Splenomegaly.

Diagnosis

- Features of hemolysis with spherocytosis.
- Positive direct antiglobulin test.

Treatment

- *Blood transfusions*: For significant anemia.
- *Corticosteroids*: Any significant hemolysis is treated with 60 mg of prednisolone daily for 3–4 weeks and then tapered; many need maintenance therapy. Parenteral methyl prednisolone is often used in acutely ill patients.
- *Splenectomy*: Patients who do not respond to steroids and/or require large maintenance dosage are candidates for splenectomy.
- *Immunosuppressive drugs*: Like azathioprine or cyclophosphamide are used if significant hemolysis continues despite splenectomy. Intravenous gammaglobulin, danazol, cyclosporine and antithymocyte globulin are used in occasional refractory cases.
- *Folic acid supplements*: Should be given to all patients with hemolysis because of increased requirements due to increased erythropoiesis.
- *Treatment of underlying cause.*

Q. Cold antibody autoimmune hemolysis (cold hemagglutinin disease; paroxysmal cold hemoglobinuria).

- Here the antibodies causing hemolysis react best at temperatures below 37°C.
- *Two forms are recognized*: Cold hemagglutinin disease and paroxysmal cold hemoglobinuria (PCH). They are relatively rare.

Cold Hemagglutinin Disease

- It is a disorder where red cells are agglutinated at low temperature. It is a chronic insidious disease most common in adults over 50 years.

Etiology

- Cold agglutinins are nearly always IgM antibodies and protein electrophoresis may show an M band. Cold agglutinins occur in some infections and malignancies. Examples are *Mycoplasma pneumoniae*, infectious mononucleosis and lymphomas.

Clincal Features

- Patients have symptoms related to both anemia and RBC agglutination.
- Symptoms of anemia include easy fatigability, palpitations, etc.

- Symptoms related to RBC agglutination are dark, purple to gray discoloration of the skin of acral parts (finger tips, toes, nose, and ears) on exposure to cold. The color disappears upon warming of the part.
- The hemolysis is both intra- and extravascular.

Treatment

- The single most useful therapy in cold agglutinin disease is avoidance of cold. Protective clothing during cold weather, use of leather gloves and stocking, or moving to a warm climate is all that is needed.
- Cytotoxic agents, particularly cyclophosphamide and chlorambucil, are sometimes used to reduce the production of antibody in severe cases. Rituximab has been shown to be useful in severe hemolysis not responding to conventional therapy.
- Steroids are not helpful and splenectomy is also not helpful since spleen is not the site of hemolysis.
- Transfusions are rarely necessary. Blood must be warmed before transfusion.
- Plasmapheresis helps in severe cases.

Paroxysmal Cold Hemoglobinuria (PCH)

- PCH is a rare disorder secondary to a cold-reacting autoantibody causing hemolysis. It occurs mainly in children and occasionally in adults.

Etiology

- Infections (secondary and tertiary syphilis, viral infections, *Mycoplasma pneumoniae and Klebsiella pneumoniae*).
- Vaccinations (measles).
- Malignancies (lymphomas and chronic lymphocytic leukemia).
- Idiopathic.

Clinical Features

- Hemolysis is precipitated by exposure to cold and is characterized by hemoglobinuria, pallor, jaundice and splenomegaly. The adult form is usually chronic, lasting several years.

Diagnosis

- The diagnosis of PCH is made by the demonstration of an IgG antibody that reacts with the red cell at reduced temperature but not at 37°C (Donath-Landsteiner antibody).

Treatment

- In children, PCH usually resolves spontaneously in a few weeks. Patient should be kept in a very warm environment.
- If severe hemolysis is present transfusion may be needed.
- Prednisolone (1 to 2 mg/kg per day) is also helpful to reduce hemolysis. In adults not responding to prednisolone, cyclophosphamide or azathioprine can be tried.
- Splenectomy is not helpful as spleen does not play any role in hemolysis.

Q. Paroxysmal nocturnal hemoglobinuria (PNH).

- This is a rare disorder secondary to an acquired defect in the red cell membrane which makes it sensitive to lysis by complement.
- It is characterised by hemolytic anemia, venous thrombosis, and deficient hematopoiesis.

Clinical Features

- PNH affects mainly adults and both sexes.
- Three main features of PNH are hemolytic anemia, venous thrombosis, and deficient hematopoiesis.
- Hemolysis manifests as anemia, mild jaundice and hemoglobinuria. Its nocturnal paroxysmal nature accounts for the name of this disorder. Patients usually complain of dark urine at night with partial clearing during the day. Hemolysis may be precipitated by infection, iron use, vaccination, or menstruation.
- Venous thrombosis is a frequent complication and can occur in intra-abdominal, cerebral and peripheral veins.
- Diminished hematopoiesis leads to cytopenias or aplastic anemia.
- PNH may progress into myelodysplasia or acute leukemia.

Laboratory Features

- Evidence of hemolysis includes anemia and raised indirect bilirubin. Urine may be positive for hemoglobinuria.
- Leucopenia, thrombocytopenia, and iron deficiency may be present.
- Leucocyte alkaline phosphatase (LAP) score is decreased.
- Bone marrow may be hypercellular or aplastic with depleted or normal iron store.
- HAM test (acidified serum lysis test first described by Dr HAM) and sucrose lysis test are positive. In HAM test, fresh normal serum of the patient with RBCs stilled at the bottom of a test tube is acidified and looked for hemolysis. PNH cells are more sensitive to hemolysis when serum is acidified.
- *Flow cytometry*: The state-of-the-art laboratory test is flow cytometry of the patient's blood to detect CD59 and CD55 on RBCs. Absence or reduced expression of both CD59 and CD55 on RBCs is diagnostic of PNH.

- *Fluorescent aerolysin*: This test uses fluorescently labeled bacterial toxin aerolysin to detect PNH cells. It is more sensitive than flow cytometry.

Treatment

- Management is mainly supportive, consisting of blood transfusions, folic acid supplements and iron replacement.
- Recently, eculizumab a monoclonal antibody that binds to the C5 component of complement and inhibits complement activation has been shown to reduce hemolysis and transfusion requirements in patients with PNH.
- Androgens, steroids and antithrombotic drugs are used occasionally.
- Bone marrow transplantation or hematopoietic stem cell transplantation is curative.
- Antiplatelets and anticoagulants may be required to prevent thrombosis.

Prognosis

- The mean survival is 10 years, but with good medical care many survive for longer period.
- Common causes of death include visceral thrombosis (cerebral, hepatic, portal), severe anemia, infection, hemorrhage or postoperative complications. Rarely, spontaneous remissions are described.

Q. Coombs' test (antiglobulin test).

- *Coombs' test* is used to check whether the blood contains certain antibodies which cause hemolysis.

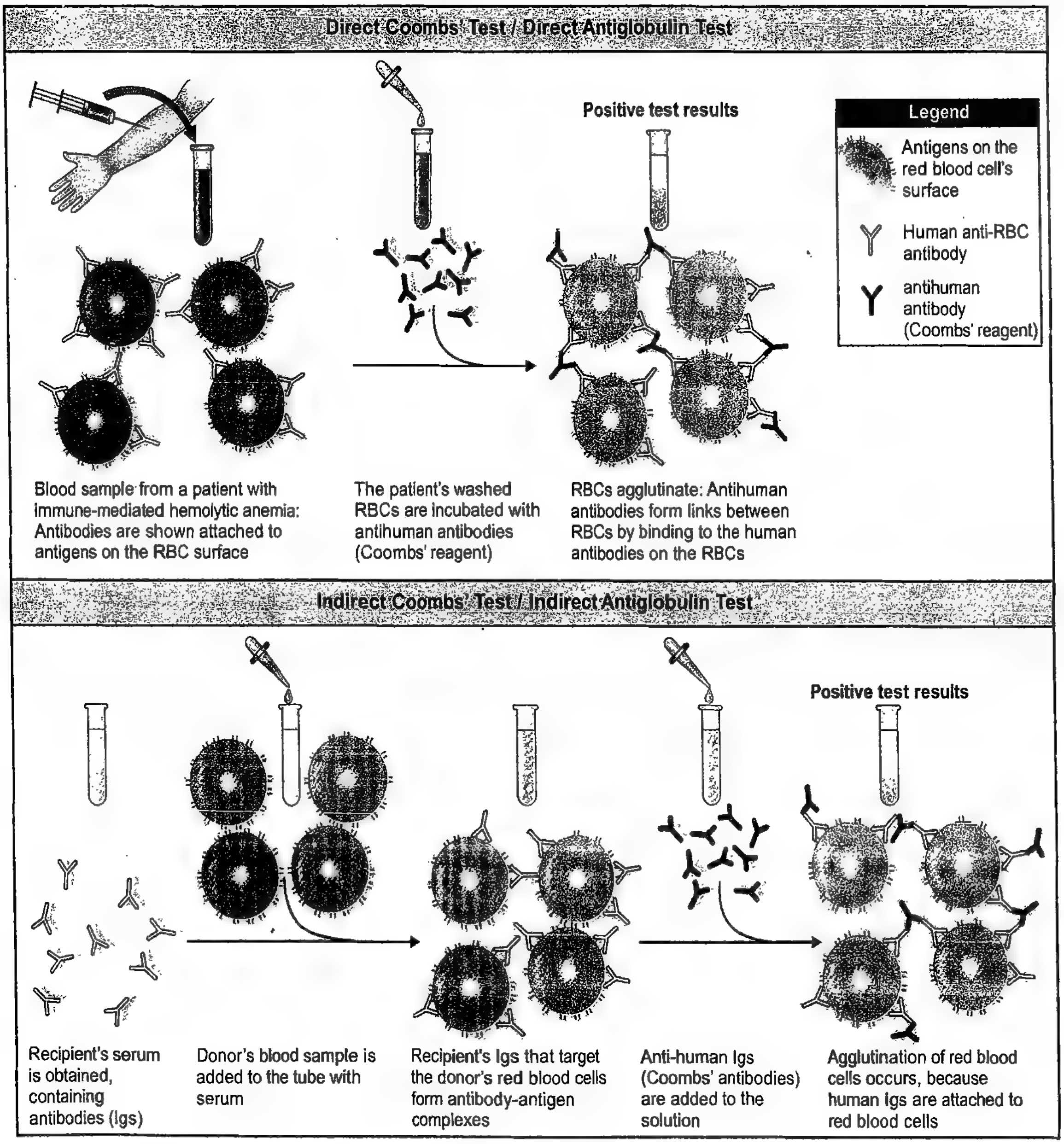

Fig. 6.2: Direct and indirect Coombs' test

- There are two types of Coombs' tests: *Direct Coombs' test* (also known as direct antiglobulin test), and the *indirect Coombs' test* (also known as indirect antiglobulin test).
- *Direct Coombs' test* is used to detect these antibodies or complement proteins that are bound to the surface of red blood cells. Direct Coombs test is used to test for autoimmune hemolytic anemia. In autoimmune hemolytic anemia, patients' blood may contain IgG antibodies that can specifically bind to antigens on the RBC surface membrane. Complement proteins may subsequently bind to the bound antibodies and cause RBC destruction. Blood sample from the patient is taken and the RBCs are washed to remove patient's own plasma and then incubated with antihuman globulin (also known as "Coombs' reagent"). If there are antibodies bound to RBC membrane, the antihuman globulin will bind to these antibodies producing agglutination of RBCs which is called positive direct Coombs' test.
- *Indirect Coombs' test* is used to detect antibodies against RBCs that are present unbound in the patient's serum. Here, the serum from the patient is incubated with RBCs of known antigenicity from other patient blood samples. If agglutination occurs, the indirect Coombs' test is positive. Indirect Coombs' test is used in prenatal testing of pregnant women, and in testing blood prior to a blood transfusion.

Q. Define aplastic anemia. Discuss the etiology, classification, clinical features, investigations and management of aplastic anemia.

Q. Drug induced aplastic anemias.

- Aplastic anemia is defined as pancytopenia with an empty (hypoplastic or aplastic) bone marrow.
- The term "aplastic anemia" is a misnomer because there is not only anemia but also thrombocytopenia and leucopenia (pancytopenia).

Etiology and Classification of Aplastic Anemia

Acquired

- Idiopathic (no identifiable cause)
- Cytotoxic drugs and radiation
- Idiosyncratic drug reaction (chloramphenicol, gold, NSAIDs and sulfonamides)
- Toxic chemicals (benzene, lindane and glue vapors)
- Viral infections (parvovirus B19, HIV infection Epstein-Barr virus)
- Immune disorders (eosinophilic fasciitis, SLE and graft versus host disease)
- Miscellaneous (paroxysmal nocturnal hemoglobinuria, thymoma and pregnancy)

Inherited

- Fanconi's anemia
- Dyskeratosis congenita
- Diamond-Blackfan anemia

Pathogenesis

- In idiopathic cases, there is no identifiable cause but in all such cases there is a stem cell defect (diminished numbers, impaired maturation, proliferation and differentiation). In all other cases, there is damage to bone marrow which may be dose-related or idiosyncratic reaction to radiation, drugs, chemicals or infectious agents.

Clinical Features

- The onset is insidious and symptoms and signs are due to anemia, leucopenia and thrombocytopenia (pancytopenia).
- Anemia causes easy fatigability, exertional dyspnea and pallor.
- Leukopenia causes recurrent infections (pneumonia, urinary tract infections, fungal infections, septicemia).
- Thrombocytopenia causes bleeding manifestations (mucosal hemorrhages, menorrhagia, and petechiae).
- Splenomegaly and lymphadenopathy are not a feature of aplastic anemia.

Investigations

- Hemoglobin is low.
- There is pancytopenia.
- Reticulocyte count is low in relation to the degree of anemia.
- ESR is elevated.
- Peripheral blood smear shows pancytopenia and normochromic-normocytic RBCs. No abnormal cells are seen in peripheral blood.
- Bone marrow examination shows profoundly hypocellular marrow with a decrease in all cell elements. The marrow space is composed mostly of fat cells and marrow stroma. The residual hematopoietic cells are morphologically normal. Malignant infiltrates or fibrosis are absent. The bone marrow iron store is normal or increased.

Prognosis

- Prognosis depends upon two factors, disease severity and patient age. Severe aplastic anemia is associated with reduced survival rate and there is a strong inverse relation between patient age and 5-year survival.

Treatment

Supportive Therapy

- Involves treatment of infection, correction of anemia with blood transfusion, correction of thrombocytopenia by platelet transfusion.
- Antifibrinolytic agents (tranexamic acid or epsilon-amino caproic acid) are also useful to control bleeding in severe cases.
- Blood and platelet transfusions should be used sparingly in patients who are candidates for hematopoietic stem cell transplantation to avoid sensitization.

Definitive Therapy

- Bone marrow transplantation—allogeneic bone marrow transplantation is curative in aplastic anemia, but is limited by the availability of an HLA-matched donor as well as graft versus host disease in patients over the age of 45 years. This is the treatment of choice in patients below 45 years if an HLA-matched donor is available.
- Immunosuppressive regimens are recommended for those above 45 years. They are not curative, but improve survival. A combination of anti-thymocyte globulin, cyclosporine, and corticosteroids with or without granulocyte-colony stimulating factor (G-CSF) can be used for immunosuppression.
- Treatment of the underlying cause or agent.

Q. Fanconi anemia.

- Fanconi anemia is the most common form of inherited aplastic anemia.
- Random breaks of chromosomes are seen due to defect in DNA repair.
- It is an autosomal recessive disorder characterized by several congenital anomalies, progressive bone marrow failure, and an increased incidence of malignancies.
- It usually presents within the first decade of life. There are skeletal (hypoplastic or absent thumb, radii) cardiac, neurologic (microcephaly, microphthalmia and mental retardation) and renal malformations with hyperpigmentation (patchy) of skin.
- Treatment involves hematopoietic stem cell transplantation, androgens and corticosteroid therapy.

Q. Erythropoietin.

Q. Ectopic sources of erythropoietin.

- Erythropoietin (EPO) is a glycoprotein growth factor which stimulates erythropoiesis, and RBC maturation.
- Erythropoietin is produced by the kidney and a small amount (<10 percent) by the liver. In the kidney interstitial fibroblasts are thought to produce erythropoietin and studies have shown that proximal tubular cells also produce erythropoietin. Hypoxia is the main stimulus for erythropoietin release which in turn stimulates RBC production.
- In patients with chronic renal failure, anemia is common due to reduced erythropoietin production. Injection of erythropoietin in chronic renal failure patients restores mormal number of RBCs and corrects anemia.
- Ectopic sources of erythropoietin include cerebellar hemangioma, uterine leiomyoma, pheochromocytoma, and hepatoma.

Recombinant Erythropoietin

- This is a synthetic (recombinant) erythropoietin available in the market. Darbepoetin alfa is an other synthetic erythropoietin analogue which has longer half life and hence can be given less frequently.

Indications for Erythropoietin Therapy

- Anemia of chronic kidney disease (most common indication).
- Less common indications are anemia of chronic disease and anemia associated with cancer chemotherapy.

Side Effects of Erythropoietin Therapy

- Hypertension
- Headache
- Influenza-like syndrome.

Q. Define neutrophilia. Enumerate the causes of neutrophilia.

- Absolute neutrophil count of more than 7,700/µl in the presence of a total WBC count less than 11,000/µl is called neutrophilia.

Causes of Neutrophilia

- Drug-induced—glucocorticoids and lithium.
- Infections—bacterial, fungal and sometimes viral.
- Inflammation—thermal injury, tissue necrosis, myocardial and pulmonary infarction, hypersensitivity states and collagen vascular diseases.
- Myeloproliferative diseases—myelocytic leukemia, myeloid metaplasia and polycythemia vera.
- Stress, excitement and vigorous exercise.
- Metabolic disorders—diabetic ketoacidosis, acute renal failure, eclampsia, acute poisoning.
- Others—metastatic carcinoma, acute hemorrhage or hemolysis.

Q. Define neutropenia and agranulocytosis. Describe the etiology, clinical features and management of neutropenia/agranulocytosis (febrile neutropenia).

- Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1500/μ.
- Agranulocytosis refers to ANC less than 500/μ.
- The risk of infection begins to increase at an ANC below 1000/μ.

Etiology

Decreased production
- Drug-induced (chemotherapeutic agents, methotrexate, chloramphenicol, clozapine and carbimazole)
- Hematologic diseases—idiopathic, cyclic neutropenia, Chédiak-Higashi syndrome and aplastic anemia.
- Tumor invasion of bone marrow (myeloma, leukemias and myelofibrosis)
- Nutritional deficiency—vitamin B_{12}, folate (especially alcoholics)
- Infections—tuberculosis, typhoid fever, brucellosis, tularemia, measles, infectious mononucleosis, malaria, viral hepatitis, leishmaniasis and AIDS

Peripheral destruction
- Hypersplenism
- Antineutrophil antibodies
- Autoimmune disorders—Felty's syndrome, rheumatoid arthritis, lupus erythematosus

Peripheral pooling (transient neutropenia)
- Overwhelming bacterial infection (acute endotoxemia)
- Hemodialysis
- Cardiopulmonary bypass

Clinical Features

- Can be asymptomatic.
- Increased risk of recurrent infections and sepsis. Common infective organisms include *Staphylococcus aureus*, gram-negative organisms and fungi.
- Common sites of infection include the oral cavity and mucous membranes, skin, perirectal and genital areas.
- Classic presentation is sore throat and fever.
- Ulcers in the throat and mouth.
- Toxemia and sepsis can lead to death.

Investigations

- Total WBC count is low.
- Neutrophil count is low.
- Peripheral smear shows absence of neutrophil and band forms.
- Bone marrow examination shows myeloid aplasia or hypoplasia or myeloid maturation arrest.
- Blood culture may grow the infective organism.
- Imaging studies such as chest X-ray, X-ray of paranasal sinuses, CT scan of the abdomen, etc. may be done based on history and examination findings to identify the focus of infection.

Treatment

- Treatment depends upon the cause and degree of the neutropenia.
- Patients with bone marrow hypoplasia and/or severe infections should receive aggressive antibacterial therapy for fever, even in the absence of signs of infection. Broad spectrum antibiotics to coverage both gram-positive and gram-negative bacteria should be used. Patients with an ANC less than 500/μl and marrow aplasia should always be treated on an inpatient basis with parenteral antibiotics.
- G-CSF (granulocyte colony stimulating factor) should be given to patients with inadequate response to antibiotics.

Q. Define pancytopenia. Enumerate the causes of pancytopenia.

- Pancytopenia refers to reduction of all three cells of blood, i.e. RBCs, WBCs and platelets. If only two types of cells are low, the term bicytopenia is used.
  - Vit B_{12}, iron and folic acid deficiency
  - Aplastic anemia
  - Leukemias (acute leukemia, hairy cell leukemia)
  - Myelodysplastic syndrome
  - Hypersplenism
  - Bone marrow infiltration by carcinoma, lymphoma, multiple myeloma, myelofibrosis, Niemann-Pick disease
  - Osteopetrosis (marble bone disease)
  - Systemic lupus erythematosus
  - Paroxysmal nocturnal hemoglobinuria
  - Disseminated tuberculosis
  - Overwhelming infections

Q. Define eosinophilia. Enumerate the causes of eosinophilia.

- Eosinophilia is defined as absolute eosinophil counts above 600 eosinophils/μl or >6% in peripheral blood.

Causes of Eosinophilia

Allergic diseases
- Atopic and related diseases (Hay fever, asthma, eczema, serum sickness, allergic vasculitis, and pemphigus)
- Drug allergy

(contd.)

Infectious diseases
- Parasitic infections (worm infestation, filariasis, Loeffler's syndrome, tropical pulmonary eosinophilia)
- Some fungal infections

Malignancies
- Hypereosinophilic syndrome
- Leukemia
- Lymphomas
- Carcinoma lung, stomach, pancreas ovary, and uterus
- Mastocytosis

Collagen vascular diseases
- Rheumatoid arthritis
- Eosinophilic fasciitis
- Allergic angiitis
- Periarteritis nodosa

Endocrine
- Hypoadrenalism

Drugs
- Sulphonamides
- Aspirin
- Nitrofurantoin
- Penicillins

Idiopathic hypereosinophilic syndrome

Q. Sideroblastic anemias.

- Sideroblastic anemias are due to deranged synthesis of heme within red cell precursors. Deranged heme synthesis leads to impaired hemoglobin production with the formation of hypochromic, microcytic and other misshaped RBCs.
- Iron cannot be utilized which accumulates inside RBCs leading to ring sideroblasts. Iron overload is also a constant feature of most sideroblastic anemias.
- Sideroblastic anemias are characterized by the presence of polychromatophilic, stippled, targeted RBCs (siderocytes).
- Sideroblastic anemias are part of a myelodysplastic syndrome but may be hereditary or may occur secondary to drugs or toxins.

Classification

Hereditary
- X-linked
- Autosomal
- Sporadic congenital

Acquired
- Pure sideroblastic anemia
- Refractory anemia with ring sideroblasts (RARS)
- Alcoholism
- Drugs (isoniazid, chloramphenicol)
- Copper deficiency
- Hypothermia

Features

- Indolent or progressive anemia.
- Microcytic hypochromic RBCs.
- Iron overload.
- Characteristic ringed sideroblasts in the bone marrow. The iron laden mitochondria surround the nucleus and appear as the pathognomonic rings with Prussian blue staining.

Diagnosis

- Sideroblastic anemia is suspected in patients with microcytic anemia, with increased serum iron, serum ferritin, and transferrin saturation.

Treatment

- Anemia responds to large doses of pyridoxine (200 mg daily for 2–3 months).
- Blood transfusions can be given for severe anemia.
- Iron overload can be treated by periodic phlebotomies and desferrioxamine.
- Recombinant human erythropoietin and GM-CSF (granulocyte-monocyte colony-stimulating factor) are helpful in selected cases.
- Bone marrow transplantation can be done in severe transfusion-dependent patients.

Q. Describe the structure and function of normal hemoglobin.

Q. Normal hemoglobins.

Hemoglobin Structure

- Hemoglobin (Hb) is a tetramer consisting of four polypeptide chains: two alpha chains and two beta chains. Alpha chain contains 141 amino acids and beta chain 146 amino acids.
- Different hemoglobins are produced during embryonic, fetal, and adult life. The major adult hemoglobin, HbA, has 2 alpha chains and 2 beta chains ($\alpha_2\beta_2$). HbF predominates during fetal life and contains 2 alpha chains and 2 gamma chains ($\alpha_2\gamma_2$). HbA_2 is found in little concentration in adults and contains 2 alpha chains and 2 delta chains ($\alpha_2\delta_2$).
- Each globin chain contains a single heme molecule, consisting of a protoporphyrin IX ring complexed with a single iron atom in the ferrous state (Fe^{2+}). Each heme molecule can bind a single oxygen molecule. Since there are four heme molecules in every molecule of hemoglobin, it can transport up to four oxygen molecules.
- The exterior surface of globin chain is hydrophilic and soluble whereas the interior forms a hydrophobic pocket

into which heme is inserted. The hemoglobin tetramer is highly soluble but individual globin chains are insoluble. Unpaired globin precipitates, forming inclusions that damage the cell. Solubility and reversible oxygen binding are affected in hemoglobinopathies.

Function of Hemoglobin

- Hemoglobin binds to oxygen at the alveolus, retains it, and releases it to tissues.

Q. Define hemoglobinopathies. How do you classify them?

- Hemoglobinopathies are disorders affecting the structure, function, or production of hemoglobin.

Classification

Hereditary hemoglobinopathies

- *Qualitative abnormality* of hemoglobin: Here the amino acid sequences in globin chains are defective which lead to altered physical or chemical properties of hemoglobin.
  For example, HbS, HbC
- *Quantitative abnormality* of hemoglobin: Here the amino acid sequence is normal, but one or more globin chains are absent.
  For example, Thalassemias.

Acquired hemoglobinopathies

- Methemoglobin
- Sulfhemoglobin
- Carboxyhemoglobin

Q. Discuss the etiology, pathogenesis, clinical features, investigations and management of sickle cell anemia.

Q. Hemoglobin-S (HbS).

Q. Sickle cell crisis and its management.

Q. Splenic sequestration syndrome.

- The sickle cell anemia is characterized by the presence of HbS caused by a mutation in the β-globin gene that changes the sixth amino acid from glutamic acid to valine (glutamic acid goes).
- If both genes encoding for beta chain are abnormal, it is called sickle cell disease. It is more severe and is inherited as autosomal recessive manner.
- If only one gene is abnormal, and other gene is normal, it is called sickle cell trait. These patients have mild disease and can be asymptomatic.

Pathophysiology

- RBCs containing HbS turn into sickle shaped cells on deoxygenation. Other factors leading to sickling are fever, sluggish blood flow, and acidosis. Sickling happens due to polymerization of HbS which distort the shape of RBC.
- Sickling of RBCs leads to hemolysis causing anemia. Sickled RBCs cannot negotiate through small vasculature leading to vaso-occlusive complications such as organ damage.

Clinical Manifestations

- Clinical manifestations include anaemia (due to hemolysis), pain (due to vascular occlusion causing ischemia), infections (due to damage to spleen), and damage to organ systems.
- Growth retardation and psycho-social problems are common.
- Splenic infarcts result in frequent life-threatening episodes of septicemia. Many types of crisis such as painful crisis, splenic sequestration crisis and aplastic crisis can occur which is life threatening unless treated promptly.
- Vaso-occlusion can cause organ damage (particularly heart and kidney in adults and brain in children).
- Presence of high amount of HbF may decrease the symptoms of sickle cell disease because HbF interferes with polymerization of HbS.

Painful Crisis (Sickle Cell Crisis)

- Vascular-occlusion can lead to ischemic pain in many areas of the body. Pain is the commonest cause of debility in HbS disease. Acute episode of severe pain is called painful crisis or sickle cell crisis. Acute pain is the first symptom of disease in many paients and is the most frequent symptom after the age of two years. Acute pain is also the complication for which patients with sickle cell disease commonly seek medical attention.
- Pain may be precipitated by events such as weather conditions (e.g. high wind speed/low humidity), dehydration, infection, stress, menses, alcohol consumption, and nocturnal hypoxemia. However, the majority of painful episodes have no identifiable cause.
- Pain can affect any area of the body, but common in the back, chest, extremities, and abdomen. Dactylitis (acute pain in the hands and/or feet) is common in children.
- Pain can vary from mild to excruciating. Pain may be accompanied by systemic symptoms such as fever, tachypnea, hypertension, nausea, and vomiting.
- Painful episodes last for two to seven days.
- Frequent pain may lead to psychosocial problems, depression and interfere with daily life.

Splenic Sequestration Crisis

- Vaso-occlusion can occur within the spleen and RBCs can get trapped in the spleen. Most of the circulating red cell mass is sequestrated in the spleen and the spleen rapidly enlarges (within hours). There is marked fall in hemoglobin concentration. There is a risk of hypovolemic shock.
- The patients who are susceptible to this syndrome are those whose spleens have not yet undergone fibrosis. Splenic sequestration crisis is associated with a 10 to 15 percent mortality rate, occurring before transfusions can be given.
- Sequestration can be recurrent in survivors and hence, splenectomy is recommended after the first attack. Milder cases can be managed with transfusion and careful observation.

Aplastic Crisis

- In aplastic crisis, there is transient arrest of erythropoiesis, leading to sudden decrease in hemoglobin, and reticulocytes. Bone marrow shows decrease in red cell precursors.
- Most cases of aplastic crisis are precipitated by infections such as parvovirus B19, *Streptococcus pneumoniae*, Salmonella, streptococci, and Epstein-Barr virus. Parvovirus B19 is the most important of these.
- Affected patients require blood transfusion. Patients usually recover within a few days.

Infections

- Sickle cell patients are prone to a variety of infections. Absent splenic function (autosplenectomy due to splenic infarcts) leads to infections with the encapsulated organisms, e.g. *Strep. pneumoniae* and *H. influenzae*. Pneumococcal infections can result in death within hours.
- Urinary tract infections (due to *E. coli*) and osteomyelitis are also common. *Salmonella typhimurium* is another common infecting organism.

Specific Organ Systems Complications

- *CVS*: Anemia and vaso-occlusive phenomenon can lead to myocardial ischemia and infarction. Repeated blood transfusions can lead to iron overload and restrictive cardiomyopathy.
- *RS*: Pneumonia or pulmonary infarction.
- *CNS*: Transient ischemic attacks, strokes and cerebral hemorrhage.
- *Hepatobiliary system*: Gallstones (pigmented gallstones due to ongoing hemolysis), recurrent abdominal pain due to vaso-occlusive crisis, hepatomegaly and hepatic dysfunction.
- *Obstetric and gynecologic system*: Placental infarcts can lead to intrauterine growth retardation and low-birth-weight babies. The frequency of spontaneous abortion is high.
- *Genitourinary system*: Hematuria, urinary tract infection, hyperuricemia and gout are common. Renal failure is common in elderly people. Priapism (painful erection of penis) can occur.
- *Ocular complications*: Proliferative retinopathy.
- *Orthopedic system*: Avascular necrosis of the hip and osteomyelitis.
- *Skin*: Ulcers around the ankle.

Investigations

- *Features of hemolysis*: Mild to moderate anemia, reticulocytosis, unconjugated hyperbilirubinemia, elevated serum LDH and low serum haptoglobin.
- Peripheral blood smear reveals sickled RBCs, polychromasia indicative of reticulocytosis, and Howell-Jolly bodies reflecting hyposplenia. RBCs are normochromic.
- *Sickle test*: Sickling of RBCs occurs when mixed with a solution of sodium metabisulphite.
- Hemoglobin electrophoresis allows the definitive diagnosis of sickle cell disease. Most of the hemoglobin is HbS.
- Genetic analysis can show the specific mutation.

Management

General Measures

- Avoidance of dehydration, cold weather and hypoxia
- Psychosocial support
- Dietary advice (adequate calorie intake, folic acid, vitamin C, vitamin E and zinc).

Specific Measures

- *Infections*: Infections can be prevented by prophylactic penicillin and immunizations. Pneumococcal and *H. influenzae* vaccination should be given to all patients with sickle cell anemia. Hepatitis B vaccination is also necessary. Febrile episodes should be investigated appropriately and treated with early antibiotic therapy.
- *Pain management*: Pain should be controlled by aggressive use of analgesics. Most of the time opioid analgesics such as morphine, fentanyl or tramadol are required. Dehydration should be prevented.
- *Blood transfusions*: Transfusions can be used to correct anemia and also in emergencies such as splenic sequestration syndrome. Blood transfusion also decreases the level of HbS by dilution. However, hemoglobin should not be raised above 10 g/dl because of increases in viscosity

and the risk of vaso-occlusive episodes. Blood transfusions are associated with problems like transmission of viral diseases, iron overload and allo-immunization.

- *Hydroxyurea*: Hydroxyurea induces the synthesis of fetal hemoglobin. High levels of fetal hemoglobin (HbF) decrease the severity of crisis and prolong survival in sickle cell patients. Co-administration of hematopoietic agents such as erythropoietin along with hydroxyurea may also be useful.
- *Bone marrow transplantation* offers the only chance of cure at present.

Prognosis

- Patients now survive up to 6th or 7th decade. Common causes of death include organ failure (predominantly renal) and sickle cell crisis. A high level of HbF predicts prolonged survival.

Q. What are thalassemias? Classify thalassemias.

- Thalassaemias are a group of inherited anemias characterized by reduced or absent production of one or more globin chains of the hemoglobin.
- Thalassemia is common in the Mediterranean region especially amongst Italians and Greeks. The thalassemia belt extends to India and South-East Asia. In India, it is found in Punjab, Gujarat, Maharashtra, Karnataka, Bengal and Assam. It is relatively less common in the southern states. On an average, 3% of Indians carry the thalassemia gene (chiefly beta thalassemia). The highest incidence is found in Lohanas and Sindhis.

Classification

- Thalassemias are named according to globin chain deficiency, e.g. in beta thalassemia, there is deficiency of beta chain, and in alpha thalassemia, there is deficiency of alpha chain.

Beta thalassemias
- *Beta thalassemia major* (Cooley's anemia) (patient is homozygous, i.e. both genes defective)
- *Beta thalassemia intermedia* (here the patient is symptomatic, but can do well even without transfusions)
- *Beta thalassemia minor* (also known as thalassemia trait, patient is heterozygous, i.e. one gene defective, other gene normal)

Alpha thalassemias
- *Alpha thalassemia-2 trait* (loss of one of the four alpha globin genes)
- *Alpha thalassemia-1 trait* (loss of two of the four alpha globin genes, also known as thalassemia minor)
- *Hemoglobin H disease* (loss of three of the four alpha globin genes)
- *Hemoglobin-Barts (hydrops fetalis)* (all four alpha globin genes are non-functional)

Q. Discuss the etiology, pathogenesis, clinical features, investigations and management of thalassemia major (Cooley's anemia).

Etiology

- Beta-thalassemias usually arise from point mutations in or near the gene which encodes beta globin chain of hemoglobin. The "beta gene" cluster is located on the short arm of chromosome 11.

Pathophysiology

- Impaired synthesis of globin chain decreases the production of hemoglobin causing hypochromia and microcytosis. There is accumulation of unaffected globin chains since their production proceeds at a normal rate.
- In the presence of reduced β chains, the excess alpha chains are unstable and precipitate, leading to damage of red blood cell membranes. This leads to intramedullary (in the bone marrow) and peripheral hemolysis causing anemia.
- Anemia leads to bone marrow hyperplasia and ineffective erythropoiesis resulting from the intramedullary destruction of the developing erythroid cells.
- Marked expansion of the bone marrow may cause severe bony deformities, osteopenia, and pathologic fractures.

Clinical Features

- Symptoms start late in the first year of life when fetal hemoglobin levels decline.
- Pallor, irritability, growth retardation, hepatosplenomegaly and jaundice develop due to severe hemolytic anemia.
- Anemia and hemolysis stimulate erythropoiesis leading to extensive marrow expansion leading to characteristic chipmunk facies (frontal bossing and prominent check bones).
- 80% of untreated children die within the first five years of life as a result of severe anemia, high output heart failure, and infections.
- Repeated blood transfusions can lead to iron overload. Many patients die secondary to iron overload-related cardiomyopathy or arrhythmias.
- Various endocrinological abnormalities such as delayed puberty, diabetes mellitus, hypoparathyroidism and hypothyroidism can occur due to iron overload.
- Repeated blood transfusions can lead to transmission of viruses (HBV, HCV, and HIV).

Table 6.2 Differences between β-thalassemia major and minor

Features	β-thalassemia major	β-thalassemia minor
• Symptoms	Symptomatic	Asymptomatic
• Genes resposnsible for globin chain synthesis	Both defective	One is normal and one is defective
• Anemia	Severe	Mild
• Peripheral smear	Severe hypochromasia, microcytosis and erythroblastosis	Mild hypochromasia and microcytosis, a few target cells and punctate basophilia
• Hb electrophoresis	HbF elevated HbA reduced/absent	HbA2 elevated
• Parents	Both having thalassemia minor	One parent having thalassemia minor

Investigations

- Signs of hemolysis such as anemia, increased indirect (unconjugated) bilirubin, increased LDH and reduced haptoglobin levels.
- HbA is markedly reduced and HbF is raised.
- Peripheral smear shows hypochromia, microcytosis, anisopoikilocytosis, tear drop cells and target cells. Nucleated red cells are abundant but reticulocyte count is low due to ineffective erythropoiesis. RBCs show clumped inclusion bodies representing precipitates of alpha globin within the red cell. These precipitates (Heinz bodies) can be stained with methyl violet or other supravital stains. WBC and platelet counts are normal unless hypersplenism develops.
- Bone marrow shows marked hypercellularity.
- Serum iron and transferin saturation are increased due to high red cell turnover.
- The osmotic fragility test is significantly reduced.
- Skull X-ray shows widened diploic space and hair-on-end appearance. Compression fractures of the vertebrae and marked osteoporosis are common.

Management

- Beta thalassaemia major requires regular blood transfusions to maintain hemoglobin at >10 g/dl. Correction of anemia leads to normal growth and development.
- Repeated blood transfusions lead to iron overload. Hence, iron chelation therapy should be given (desferrioxamine infusion subcutaneously over 8–10 hours a day, 5 days a week or oral iron chelator deferiprone).
- Folic acid supplements should be given to all patients because of increased requirements due to increased red cell turnover.
- Splenectomy for gross symptomatic splenomegaly or hypersplenism.
- Allogeneic bone marrow transplantation is the treatment of choice for β-thalassemia major and can cure it.
- Alternative forms of therapy include manipulation of globin gene expression using butyrate and gene therapy.
- Genetic counseling and prenatal diagnosis should be offered to affected parents.
- Thalassemia minor requires no treatment except genetic counseling, avoidance of inappropriate iron therapy and close monitoring during pregnancy.

Q. Hereditary spherocytosis.

- Hereditary spherocytosis is the commonest hemolytic anemia secondary to membrane defect.
- It is usually inherited as an autosomal dominant condition, although 25% of cases have no family history and represent new mutations.

Pathology

- It is due to a defective structural protein (spectrin) of the red cell membrane. Other defective membrane protiens are ankyrin and band 3 protein. All these protein defects lead to reduced surface area of RBCs which lose their biconcave shape and become spherical. The morphologic hallmark of HS is the microspherocyte, which is caused by loss of RBC membrane surface area and has abnormal osmotic fragility in vitro. As the spherical cells are unable to pass through the splenic microcirculation, they die prematurely.

Clinical Features

- Signs and symptoms of hereditary spherocytosis (HS) include mild pallor, intermittent jaundice, and splenomegaly.
- Most cases are associated with an asymptomatic compensated chronic hemolytic state.
- A hemolytic crisis can occur when the severity of hemolysis increases; this is seen in association with infection.
- A megaloblastic crisis can occur due to folate deficiency which is common during pregnancy.

- An aplastic crisis occurs in association with parvovirus B-19 infection.
- Pigment gallstones are present in up to 50% of patients and may cause symptomatic cholecystitis.

Investigations

- Anemia.
- Reticulocytosis.
- Peripheral smear shows spherocytes.
- LFT shows rise in indirect bilirubin.
- Serum LDH level is raised.
- Direct Coombs' test is negative excluding immune hemolysis.
- Osmotic fragility test shows increased sensitivity to lysis in hypotonic saline solutions.

Management

- Folic acid prophylaxis, 5 mg once weekly, should be given for life.
- Splenectomy may be considered in severe hemolysis.
- Acute, severe hemolytic crises require blood transfusions.

Q. Glucose-6-phosphate dehydrogenase deficiency.

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme defect associated with hereditary hemolytic anemia. It is an X-linked disorder, hence seen mostly in males. Females are protected because of two X-chromosomes one of which can carry normal gene.

Pathogenesis

- G6PD is the first enzyme in the hexose monophosphate shunt pathway which generates NADPH. NADPH is required to keep the glutathione in reduced state in RBCs.
- Depletion of cellular glutathione results in damage to RBCs by oxidizing agents and various drugs leading to hemolysis.

Precipitating Causes of Hemolysis in G6PD Deficiency

- *Drugs*: Primaquine, quinine, sulfonamides, dapsone
- Diabetic ketoacidosis
- Favabeans
- Viral and bacterial infections.

Clinical Features

- Hemolysis usually occurs only under oxidant stress.
- Hemolysis is usually precipitated by infections due to liberation of oxidant molecules by granulocytes and mononuclear phagocytes and oxidant drugs. Ingestion of fava beans (Italian broad beans) can also cause hemolysis in some patients due to the presence of high levels of oxidant pyrimidine analogues in the beans.
- Hemolysis leads to anemia, reticulocytosis, hemoglobinuria, hyperbilirubinemia, and jaundice. Hemoglobinuria can cause renal tubular necrosis and renal failure.
- Many neonates with G6PD deficiency manifest jaundice at 1 to 4 days of age which usually responds to phototherapy.

Investigations

- Evidence of intravascular hemolysis after infections and certain drugs.
- Estimation of G6PD activity in the RBC.

Treatment

- Asymptomatic individuals require no treatment.
- Mild hemolytic episodes are treated by withdrawing the offending drug, or treatment of the concurrent infection.
- Severe hemolytic episodes may require red cell transfusions to correct anemia and measures to prevent renal failure due to hemoglobinuria.

Q. Methemoglobinemia.

- Methemoglobin is an altered state of hemoglobin in which the ferrous (Fe^{2+}) ions of heme are oxidized to ferric (Fe^{3+}) state. Methemoglobin is unable to bind oxygen. Hence, oxygen delivery to the tissues is impaired.
- Normally a small amount of methemoglobin is formed daily which is reduced back to normal hemoglobin by cytochrome b5 reductase and glucose-6-phosphate dehydrogenase (G6PD).

Causes

- Methemoglobinemia can occur due to congenital or acquired causes.
- Most cases are acquired, due to increased methemoglobin formation by various agents such as dapsone, benzocaine, etc.
- Hereditary methemoglobinemia is due to deficiency of reducing enzymes such as cytochrome b5 reductase. Another congenital cause of methemoglobinemia is hemoglobin M disease.

Clinical Features

- Chronic methemoglobinemia is asymptomatic most of the time. Some may complain of headache and easy fatigability. The main complaint is "cyanosis" or slate-blue color of the skin and mucous membranes. Cyanosis is present when the methemoglobin concentration exceeds 1.5 g/dl.
- Patients with acute methemoglobinemia are usually symptomatic due to acutely impaired oxygen delivery to tissues. Symptoms include headache, fatigue, dyspnea, and lethargy. At higher methemoglobin levels, respiratory depression, altered consciousness, shock, seizures, and death may occur.

Diagnosis

- Methemoglobinemia should be suspected when there is "cyanosis" in the presence of normal PaO_2 as obtained by arterial blood gases. Levels of methemoglobin should be measured in lab.

Treatment

- All patients with hereditary methemoglobinemia should avoid exposure to aniline derivatives, nitrates, and other agents which can induce methemoglobinemia. Methylene blue or ascorbic acid orally may be useful in cytochrome b5R deficiency. Riboflavin has also been shown to be useful.
- In acquired methemoglobinemia any offending agent should be discontinued. In severe methemoglobinemia blood transfusion or exchange transfusion and intravenous methylene blue are helpful. However, methylene blue is not helpful in patients with G6PD deficiency, since the reduction of methemoglobin by methylene blue is dependent upon NADPH generated by G6PD.

Q. Kernicterus.

- Kernicterus refers to brain damage caused by unconjugated bilirubin deposition in basal ganglia and brainstem nuclei, caused by either acute or chronic hyperbilirubinemia. It occurs in neonates due to hyperbilirubinemia of various reasons. Neurologic sequelae develop during the first year after birth.
- *The major features of kernicterus include*: Choreoathetoid cerebral palsy (chorea, ballismus, tremor), sensorineural hearing loss, gaze abnormalities (especially limitation of upward gaze), dental-enamel dysplasia. Cognitive function is usually spared.
- There is no treatment for established kernicterus. It should be prevented by early recognition and treatment of hyperbilirubinemia.

Q. Etiology of leukemias.

Idiopathic

- Majority of cases are idiopathic

Ionizing radiation

- Atomic bombing
- X-ray exposure
- Radiotherapy

Viruses

- Human T cell lymphotropic virus type I (HTLV-I) (can cause adult T cell leukemia)
- HTLV-II (causes a syndrome resembling hairy cell leukemia)
- Epstein-Barr virus

Immunological

- Immune deficiency states (e.g. HIV and hypogammaglobulinemia) are associated with an increase in hematological malignancy

Genetics factors

- Identical twins
- Trisomy 21 (Down syndrome)
- Trisomy 13 (Patau)
- XXY (Klinefelter syndrome)
- Disorders causing chromosomal instability (Bloom syndrome, Fanconi's anemia, and ataxia-telangiectasia)

Chemicals and drugs

- Exposure to benzene and benzene-containing compounds
- Exposure to tobacco, chemotherapeutic agents (especially cyclophosphamide, melphalan, other alkylating agents, and etoposide)

Chromosomal translocations

- For example, translocation between 9 and 22 chromosomes causing CML

Chromosomal disorders

- Fanconi's anemia, Down syndrome, Bloom syndrome, ataxia-telangiectasia

Q. Classification of leukemias.

Acute leukemias

- Lymphoid (lymphoblastic)
- Myeloid (myeloblastic)

Chronic leukemias

- Lymphoid (lymphocytic)
- Myeloid (myelocytic)

Classification of acute leukemias (French-American-British (FAB) classification).

Acute lymphoblastic leukemia (ALL)

- L1—Lymphoblasts with uniform, round nuclei and scant cytoplasm
- L2—More variability of lymphoblasts, sometimes irregular nuclei with more cytoplasm than L1
- L3—Lymphoblasts with finer nuclear chromatin and blue to deep blue cytoplasm that contains vacuoles

Acute myeloid leukemia (AML)

- M0—Acute undifferentiated leukemia
- M1—AML with minimal differentiation
- M2—AML with differentiation
- M3—Acute promyelocytic leukemia
- M4—Acute myelomonocytic leukemia
- M5—Acute monocytic leukemia
- M6—Acute erythroleukemia
- M7—Acute megakaryocytic leukemia

Classification of chronic leukemias

Chronic lymphoid leukemia

B cell

- Chronic lymphocytic leukemia (CLL)
- Prolymphocytic leukemia (PLL)
- Hairy cell leukemia (HCL)
- Plasma cell leukemia

T cell

- Large granular lymphocytic leukemia
- T cell prolymphocytic leukemia (T-PLL)
- Adult T cell leukemia/lymphoma

Chronic myeloid leukemia

- Ph. positive
- Ph. negative, BCR positive
- Ph. negative, BCR negative
- Eosinophilic leukemia

Ph = Philadelphia chromosome, BCR = Breakpoint cluster region

Q. Define acute leukemia. Discuss the etiology, clinical features, investigations and management of acute leukemia.

Q. Discuss the etiology, clinical features, investigations and management of acute myeloblastic leukemia.

Q. Differentiation between acute lymphoblastic leukemia and acute myeloblastic leukemia (ALL and AML).

Q. Aleukemic leukemia.

- Acute leukemia is defined as a malignant clonal proliferation of lymphoid or myeloid precursor cell which replace the marrow and ultimately spill over to the peripheral blood and infiltrate lymph nodes, spleen, liver or other organs.
- Normally hematopoietic stem cells proliferate and differentiate into various cellular components of blood. In acute leukemia an early hematopoietic precursor fails to differentiate and instead continues to proliferate in an uncontrolled fashion. As a result, immature myeloid (in AML) or lymphoid cells (in ALL), called *blasts*, rapidly accumulate and progressively replace the bone marrow which in turn results in decreased production of normal red cells, white cells, and platelets (pancytopenia). Eventually leukemic blasts will pour out into the blood and also infiltrate lymph nodes, spleen, and other vital organs. Acute leukemia is rapidly fatal and most patients die within months of diagnosis. However, in many patients it can be controlled or cured with appropriate therapy.

Incidence

- The incidence in the West varies from 3 to 13 per 100,000 per year. Acute leukemia is more common in adult males. ALL (acute lymphoblastic leukemia) is more common in children and AML (acute myeloid leukemia) is more common in adults.

Etiology

- *See* previous page (etiology of leukemias).

Clinical Features

- Two things happen in leukemia which causes all the signs and symptoms. One is leukemic blasts fill the bone marrow and interfere with its function. Another is leukaemic blasts infiltrate normal organs and lead to their dysfunction.
- Decreased bone marrow function leads to deficiency of all three cell lines causing anemia, thrombocytopenia granulocytopenia. Anemia is present at diagnosis in most patients and causes fatigue, pallor, and headache and in severe cases angina or heart failure. Thrombocytopenia causes bleeding manifestations in the form of petechiae, ecchymoses, bleeding gums, epistaxis, or hemorrhage. Granulocytopenia results in increased incidence of infections.
- Infiltration of normal organs by leukemic blasts lead to enlargement of lymph nodes, liver, and spleen. Bone pain may be present and is due to leukemic infiltration of the periosteum or expansion of the medullary cavity. Leukemic cells sometimes infiltrate the skin and result

Table 6.3 Differences between AML and ALL

Features	AML	ALL
• Cell linage	Myeloid precursors	Lymphoid precursors
• Auer rods	Present	Absent
• Age group affected	Commonly adults	Commonly children
• Common genetic abnormalities	t(8;21), t(15;17), and inv(16) (p13;q22).	t(9;22) and t(4;11).
• Nuclear enzyme, terminal deoxynucleotidyl transferase (Tdt) in leukemic blasts	Rarely present	Present in more than 90%
• Lymphadenopathy	Uncommon	Common
• Hepatosplenomegaly	Uncommon	Common
• CNS involvement	Uncommon	Common
• Cytochemical staining (myeloperoxidase and sudan black B)	Positive	negative

in a raised, nonpruritic rash, a condition termed *leukemia cutis*. Leukemic cells may infiltrate the leptomeninges and cause leukemic meningitis manifesting as headache and nausea. In advanced cases, cranial nerve palsies, other neurological deficits and seizures may develop. In AML, collections of leukemic blast cells, often referred to as *chloromas* or *myeloblastomas*, can occur in virtually any soft tissue and appear as rubbery, fast-growing masses.

- Certain clinical manifestations are unique to specific subtypes of leukemia. For example, DIC (disseminated intravascular coagulation) is common in promyelocytic leukemia (AML-M3) due to release of tissue thromboplastins by leukemic cells when they die.

Laboratory Findings

- Anemia and thrombocytopenia.
- Total leucocyte count is markedly raised (often as high as 100,000/mm^3).
- Peripheral blood smear shows circulating blasts. However, blasts may not always be seen in peripheral smear ("aleukemic leukemia").
- Bone marrow is usually hypercellular with the presence of blasts. More than 20% blasts are required to make a diagnosis of acute leukemia.
- Serum LDH, uric acid and alkaline phosphatase levels are elevated due to rapid cell turnover.
- Patients with ALL (especially T cell) may have a mediastinal mass visible on chest radiograph.
- The Auer rod, an eosinophilic needle-like inclusion in the cytoplasm, is pathognomonic of AML. AML is categorized on the basis of morphology and histochemistry as M1-M7.
- ALL is diagnosed when there is no morphologic or histochemical evidence of myeloid or monocytic lineage. The diagnosis of ALL is confirmed by demonstrating surface markers of primitive lymphoid cells, by flow cytometry and monoclonal antibodies.
- Cytogenetic studies reveal many chromosome abnormalities which can also predict the prognosis in acute leukemias.

Treatment

- Chemotherapy is the mainstay of therapy for acute leukemias. The aim of chemotherapy is to induce remission and maintain it. The type of initial chemotherapy depends on the subtype of leukemia.

AML

- Most patients with AML except acute promyelocytic leukemia are treated with a combination of daunorubicin, cytarabine and etoposide. Acute promyelocytic leukemia is treated with an daunorubicin plus tretinoin. Arsenic trioxide has been shown to increase the cure rate of promyelocytic leukaemia when added to primary therapy.
- After remission induction, further therapy with curative intent includes standard chemotherapy and autologous or allogeneic bone marrow transplantation. If the leukemia recurs after initial chemotherapy, the prognosis is worse.

ALL

- ALL is treated with combination chemotherapy, including daunorubicin, vincristine, prednisone, and asparaginase. For patients with Philadelphia chromosome-positive ALL, imatinib (or dasatinib) should be added to initial chemotherapy. As with AML, patients may be treated with either chemotherapy or high-dose chemotherapy plus bone marrow transplantation.

Prognosis

- 70–80% of patients under 60 years with AML achieve complete remission. 30–40% of these patients can be cured by high-dose post-remission chemotherapy. The remission and cure rate for older patients is low. Allogeneic bone marrow transplantation is curative in 50–60% cases in young people.

Q. Leukemoid reaction.

- In severe infections, and various toxic states, total leucocyte count may go very high (exceed 50,000/cumm). Immature white cell precursors (blasts) are found in the peripheral smear. All these features resemble leukemia and hence called leukemoid reaction.

Differentiation from leukemia

- Counts are usually less than 1 lakh.
- Bone marrow is normal.
- Leucocyte alkaline phosphatase score (LAP) is increased.
- There is left shift as evidenced by presence of myelocytes and metamyelocytes
- Presence of toxic granules in neutrophils.
- Band forms may be seen.
- Basophilia and eosinophilia are not seen in leukemoid reaction.
- Treatment of underlying condition corrects the leucocyte counts.

Q. Discuss the pathophysiology, clinical features, investigations and management of chronic myeloid leukemia (CML).

Q. Peripheral smear in chronic myeloid leukemia.

Q. Philadelphia chromosome.

Q. Imatinib mesylate.

- Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by overproduction of myeloid cells.

Pathophysiology

- CML is characterized by a specific chromosomal abnormality, called the Philadelphia chromosome which occurs due to reciprocal translocation between the long arms of chromosomes 9 and 22. The abnormal chromosome 22 is known as Philadelphia chromosome.
- The oncogene *c-abl*, normally situated in the long arm of chromosome 9, gets translocated to chromosome 22, where a specific gene called *bcr* (breakpoint cluster

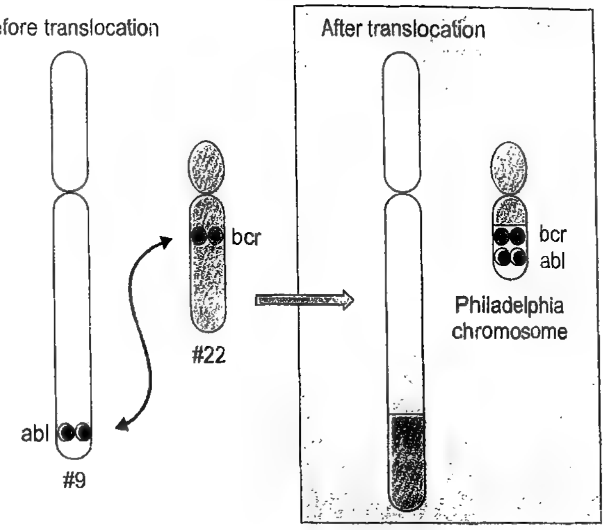

Fig. 6.3: Philadelphia chromosome

region) is situated. Both *abl* and *bcr* form a fusion gene, *abl/bcr*, which is important in the pathogenesis of CML. The fusion gene *bcr/abl* produces a protein possessing tyrosine kinase activity. This leads to tumour cell proliferation and inhibition of apoptosis.

- Patients who are Philadelphia chromosome negative tend to be older, mostly male and respond poorly to treatment.

Natural Course

- The disease has 3 stages: (1) Chronic stable phase, (2) accelerated phase and (3) blast crisis.
- The chronic phase is characterized by a large increase in peripheral blood leukocytes. Most patients are in stable phase at presentation. This phase may last months to years.
- In accelerated phase neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control. There is worsening anemia, progressive thrombocytopenia or thrombocytosis, persistent or worsening splenomegaly, clonal evolution, increasing blood basophils, and increasing marrow or blood blasts.
- In blast crisis, myeloid or lymphoid blasts fail to differentiate and large number of blasts is found in peripheral blood. Blast crisis carries very poor prognosis. Blasts in blood or marrow increase to >20%.

Clinical Features

- CML has an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance. CML is a disorder of middle age (median age at presentation is 50 years).
- The clinical hallmark of CML is not only the uncontrolled production of maturing granulocytes, predominantly neutrophils, but also eosinophils and basophils.

- Patients usually present with fatigue, weight loss, night sweats, and low-grade fever due to the hypermetabolic state caused by overproduction of white blood cells.
- Bleeding episodes are common due to platelet dysfunction.
- Abdominal fullness, early satiety, left upper quadrant pain, and discomfort may be complaned of due to massive splenomegaly.
- Acute gouty arthritis may be present due to overproduction of uric acid.
- Extremely high leukocyte counts may cause symptoms due to hyperviscosity such as priapism, respiratory distress, visual blurring, and altered mental status.
- Examination reveals pallor, massive splenomegaly, and sternal tenderness due to bone marrow hyperplasia. Hepatomegaly may also be present.

Laboratory Findings

- Anemia is usually present.
- Total WBC count is usually above 1 lakh/µl.
- Platelet count is normal or elevated.
- Absolute basophilia and eosinophilia are almost always present.
- Peripheral blood smear shows presence of myelocytes and metamyelocytes. RBC morphology is normal.
- Bone marrow aspiration and biopsy in patients with CML in chronic phase shows myeloid hyperplasia, increase in reticulin fibers and vascularity. There is increase in the myeloid-to-erythroid ratio in the bone marrow as well as a marked increase in the number of megakaryocytes and the number of more immature forms. Blast crisis is diagnosed when blasts are more than 20% in the bone marrow.
- The diagnosis of CML is established by demonstration of the Philadelphia chromosome or the BCR-ABL fusion gene. BCR-ABL can be detected in the peripheral blood by polymerase chain reaction (PCR) test, which has now supplanted cytogenetics.

Treatment

Tyrosine Kinase Inhibitors (Imatinib Mesylate, Dasatinib, Nilotinib)

- The treatment of CML has been revolutionised by the introduction of tyrosine kinase inhibitors such as imatinib mesylate, which inhibit the tyrosine kinase activity of the *BCR/ABL* oncogene. Imatinib inhibits proliferation and induces apoptosis in cells positive for *BCR/ABL*. Tyrosine kinase inhibitors are the first line drugs for chronic and accelerated phase of CML. Imatinib is well tolerated and controls the disease in 98% of chronic phase patients with positive Philadelphia chromosome. In chronic phase of CML, the dose of imatinib is 400 mg orally daily. Side effects are nausea, periorbital swelling, edema, rash, and myalgia. Blood counts normalize and splenomegaly regresses within several weeks, usually within 3 months. Philadelphia chromosome becomes negative within 6 months (maximum 12 months). Dasatinib is an other agent which is effective in patients not responding to imatinib. However, tyrosine kinase inhibitors imatinib does not cure the patient. It controls the disease as long as it is given.

Omacetaxine

- Omacetaxine is a new drug introduced for the treatment of CML. It is a protein translation inhibitor that is indicated for chronic- or accelerated-phase CML with resistance and/or intolerance to 2 or more tyrosine kinase inhibitors.

Busulfan or Hydroxyurea

- These agents suppress the bone marrow and reduce the leukocyte count. Conventional treatment of CML in chronic phase has been single agent therapy with busulphan or hydroxyurea. However, due to the availability of newer agents such as imatinib, these agents are being used less commonly now.
- Hydroxyurea is preffered over busulphan. It is given in a dose of 20–30 mg/kg od orally daily. Blood counts should be monitored and the dose is adjusted as per the counts. WBC counts recover within a short time after discontinuation of the drug.
- Busulfan is given in a dose of 6–8 mg daily orally and reduced as the leucocyte count falls. It should be discontinued when the leucocyte count falls below 20,000/µl and resumed if the count reaches 50,000/µl.

Interferon Therapy

- Alpha IFN inhibits the late progenitors which may be the major phase of CML clonal expansion. Patients with early chronic phase respond better. Reduction of '*bcr-abl*' oncogene expression has been reported after therapy with IFN. Complete hematological response is seen in 35–85% of patients. Side effects include influenza-like symptoms, lethargy, poor memory, and myalgias. However, due to the availability of newer agents such as imatinib, interferon alpha is now used only for refractory cases in combination with other agents.

Allogeneic Bone Marrow Transp antation or Stem Cell Transplantation

- If the patients do not respond to imatinib, this is the 2nd choice of therapy. The best results (80% cure rate) are obtained in patients under 40 years of age if transplanted

within 1 year after diagnosis. Bone marrow should be obtained from HLA matched siblings.

Leukapheresis

- Leukapheresis is sometimes used to control the number of WBCs in emergency situations. It is useful in two types of patients: the hyperleukocytic patient in whom rapid cytoreduction can reverse symptoms and signs of leukostasis (e.g. stupor, hypoxia, tinnitus, papilledema, priapism), and in the pregnant patient with CML who can be controlled by leukapheresis treatment without other drugs which can cause damage to the fetus.

Anagrelide

- Anagrelide can be used to decrease very high platelet count not responding to imatinib alone.

Course and Prognosis

- In the past, median survival was 3–4 years. However, after the introduction of imatinib mesylate, 4 year survival and remission is 80%.

Q. Accelerated phase of CML.

- Clinical features that signal the conversion of the chronic to the accelerated phase include unexplained fever, bone pain, weakness, night sweats, weight loss, and loss of sense of well-being, arthralgias, or left upper quadrant pain.
- Localized or diffuse lymphadenopathy may develop.
- Increase in spleen size.
- Anemia worsens.
- Increasse in leukocyte count with blasts 10–19% in peripheral blood.
- Increase in basophil count (>10%).
- Poor response to therapy.
- Drug of choice for treatment of accelerated phase is one of the tyrosine kinase inhibitors such as imatinib.

Q. Blast crisis in CML.

- Blast crisis represents transformation of CML into an acute leukemia (myeloblastic or lymphoblastic). A variety of mutations has been associated with progression to blast crisis. Mutations of the BCR-ABL tyrosine kinase domain have been observed in up to 80% of patients.
- Blast crisis can develop from days to decades after diagnosis of CML.
- Clinical features include fever, hemorrhage, generalized lymphadenopathy, abrupt increase in spleen size, bone pain and sternal tenderness.
- Peripheral smear or bone marrow shows more than 20% blasts.

Treatment of Blast Crisis

- Patients in myeloid blast crisis can be treated with acute myeloid leukemia (AML) induction chemotherapy regimens (daunorubicin, cytarabine and etoposide) in combination with a tyrosine kinase inhibitor; some patients can be treated with a TKI alone. Stem cell transplantation can also be considered at this phase.

Q. Discuss the types, clinical features, investigations, clinical staging and management of chronic lymphocytic leukemia (CLL).

- Chronic lymphocytic leukemia (CLL) is a clonal malignancy of B lymphocytes. It is characterized by a progressive accumulation of functionally incompetent lymphocytes which respond poorly to antigenic stimulation.

Pathophysiology

- 98% of cases of CLL are of B cell origin (CD5+ B type lymphocytes). In 2 to 3% of cases, malignant lymphocytes can be of T cell origin.
- Malignat lymphocytes multiply and accumulate in the bone marrow initially and subsequently spill over to blood and infiltrate lymph nodes and lymphoid organs leading to hepatomegaly and splenomegaly.
- As CLL progresses, abnormal hematopoiesis results in anemia, neutropenia, and thrombocytopenia.
- The abnormal B-lymphocytes cannot produce immunoglobulins leading to hypogammaglobulinemia and increased susceptibility to infections.

Clinical Features

- CLL is a disease of older patients, and most cases occur after the age of 50 years. Peak age is around 65 years. It is more common in Western countries.
- More in males than females (2:1).
- Many patients are asymptomatic and the diagnosis is suspected when lymphocytosis is noted on routine blood testing. Others present with fatigue or lymphadenopathy.
- On examination, most patients will have generalized lymphadenopathy and 50% will have splenomegaly.
- Recurrent infections are common due to immunodeficiency.
- CLL usually runs a slow course, but some subtypes may behave aggressively.

Staging

- A staging system (Rai system) has been developed for CLL which is as follows:

Stage 0: Absolute lymphocytosis of >10,000/μl in blood and ≥30% lymphocytes in bone marrow

***Stage I*:** Stage zero plus lymphadenopathy

Stage II: Stage zero plus hepatomegaly or splenomegaly

Stage III: Stage zero plus anemia (Hb <11gm/dl)

Stage IV: Stage zero plus thrombocytopenia (<1 lakh)

Laboratory Findings

- The white blood count is usually greater than 20,000/μl and may be markedly elevated to several hundred thousand.
- The hallmark of CLL is isolated lymphocytosis. Usually more than 75% of the circulating cells are lymphocytes. Lymphocytes resemble normal small lymphocytes, but few large and activated lymphocytes may be seen.
- RBC count and platelet count is usually normal initially but may decrease in advanced disease.
- Bone marrow shows infiltration with lymphocytes.
- Immunophenotyping demonstrates B-lymphocyte markers such as CD5+.
- Lymph node biopsy shows well differentiated, small, non-cleaved lymphocytes.
- Hypogammaglobulinemia is present in many patients and becomes more common with advanced disease.

Treatment

- A common treatment of choice is the combination of fludarabine plus rituximab. Fludarabine plus cyclophosphamide is also effective. Chlorambucil was the drug of choice earlier, and remains a reasonable first choice for elderly.
- Ibrutinib is a novel, oral inhibitor of the enzyme Bruton tyrosine kinase which is required for the activation of several B cell mediated pathways that enhance survival of CLL cells. Ibrutinib appears to be highly active in CLL and has induced durable remissions in some patients with relapsed or refractory CLL. Its role as a single agent or as part of combination chemotherapy is evolving.
- Patients with immunosuppression and recurrent bacterial infections may benefit from prophylactic infusions of gamma globulin given every month.
- Allogeneic bone marrow transplantation is potentially curative and can be offered to those whose disease cannot be controlled by standard therapies.

Prognosis

- In the past, median survival was 6 years. However, newer therapies have improved the prognosis. Patients with stage 0 or stage I disease have a median survival of 10–15 years.
- Patients with stage III or stage IV disease have a 2-year survival of greater than 90% with newer therapies.

Q. Hairy cell leukemia.

- Hairy cell leukemia (HCL) is an uncommon chronic B-cell lymphoproliferative disorder. The malignant lymphocytes have characteristic hair like cytoplasmic projections on their surface, hence called hairy cell leukaemia.

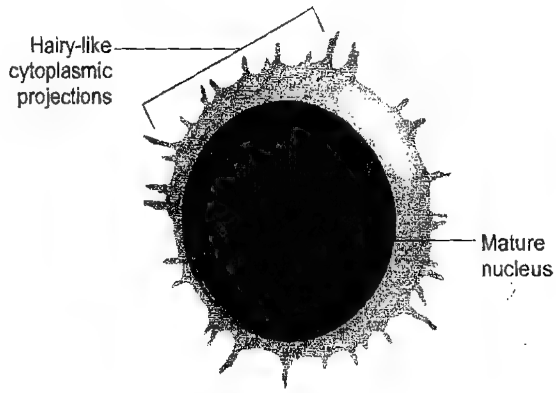

Fig. 6.4: Hairy cells with cytoplasmic projections

Etiology

- The etiology of HCL is unknown, although ionizing radiation, Epstein-Barr virus, organic chemicals, woodworking, and farming have been mentioned as possible causes.

Clinical Features

- The median age at onset is 52.
- More common in males than females (5 : 1).
- Patients may present with fatigue, weakness and weight loss.
- Bleeding manifestations due to thrombocytopenia.
- Recurrent infections due to leukopenia.
- Massive splenomegaly.
- Hepatomegaly and lymphadenopathy are uncommon.

Laboratory Findings

- There is anemia, thrombocytopenia and leucopenia (pancytopenia).
- The characteristic "hairy cells" are usually present in small numbers on the peripheral blood smear and have numerous cytoplasmic projections.

- Bone marrow is usually inaspirable (dry tap), but biopsy shows hypercellular marrow and hairy cell infiltration.
- Immunophenotyping shows B cell markers on malignant cells.

Treatment

- The treatment of choice is cladribine which is a purine analog. It is given at a dose of 0.14 mg/kg daily for 7 days. Cladribine accumulates in lymphoid cells and kills them because they are rich in deoxycytidine kinase. Complete remission is seen in more than 80% of patients. Pentostatin also produces similar results, but is more cumbersome to administer.

Course and Prognosis

- With new therapies more than 95% of patients with hairy cell leukemia survive longer than 10 years.

Q. Mention the myeloproliferative disorders.

- Myeloproliferative disorders are due to clonal expansion of multipotent hematopoietic stem cell with over-production of one or more mature, functional elements of the blood.
- These conditions may evolve into acute leukemia. For example, CML may turn into AML.

These are:

- Polycythemia vera
- Idiopathic myelofibrosis
- Essential thrombocytosis
- Chronic myeloid leukemia

Q. Define polycythemia. Enumerate the causes of polycythemia.

Q. Discuss the etiology, clinical features, diagnosis and management of polycythemia vera.

- Polycythemia is defined as an increase in circulating red blood cells above normal. Polycythemia is suspected when the hemoglobin is >16.5 g/dl in women and >18.5 g/dl in men.
- Polycythemia may be absolute when the number of cells is actually increased or relative when the plasma volume is decreased without actual increase in absolute number of cells.

Etiology

Polycythemia rubra vera (primary polycythemia)

Secondary polycythemia

- High altitude
- Cyanotic congenital heart disease
- Chronic lung disease with alveolar hypoventilation
- Hemoglobinopathies which interfere with oxygen dissociation in the tissues, methemoglobinemia
- Obesity with pickwickian syndrome
- Heavy smoking
- Erythropoietin producing neoplasms (renal carcinoma, carcinoma liver, uterine fibromyomas and cerebellar hemangioblastomas)
- Endocrine abnormalities: Cushing's syndrome, and pheochromocytoma
- Drugs: Corticosteroids, and anabolic steroids

Relative polycythemia (erythropoietin levels normal)

- Dehydration and loss of plasma as in diarrhea and burns

Polycythemia Vera (PV)

- Polycythemia vera (PV) is a myeloproliferative disorder. It is a low-grade neoplastic disorder caused by clonal proliferation of erythroid precursors. Secondary polycythemia is due to some underlying disorder (*see* above).

Pathology

- PV involves increased production of all cell lines, including RBCs, WBCs, and platelets. Clonal hematopoiesis is a hallmark of PV, suggesting that a mutation of hematopoietic stem cells is the cause of proliferation. Janus kinase-2 (JAK2) gene mutation is seen in virtually all the patients with polycythemia vera. JAK2 mutation leads to sustained activation of the JAK2 protein, which causes excess cell production, independent of erythropoietin levels.
- Increase in RBC volume increases the viscosity of the blood. Increased blood viscosity leads to thrombosis and occlusion of microcirculation in many organs.
- Hemorrhages may occur due to damage to the capillaries and also dysfunction of the platelets.
- Hyperuricemia occurs due to increased red cell turnover.
- Bone marrow is hypercellular.
- As the disease progresses, anemia and myelofibrosis develop.
- Extramedullary erythropoiesis takes place in the spleen, liver and other sites.

Clinical Features

- Usually occurs above the age of 20 years and the incidence increases with age.
- Males are affected more often.
- Initial symptoms are vague, such as headache, dizziness, tinnitus, weakness, lassitude, and fatigue.
- Thrombotic manifestations range from digital ischemia to Budd-Chiari syndrome with hepatic vein thrombosis. Abdominal thromboses are particularly common. The cerebral, retinal, cardiac and/or peripheral vessels may be the seat of vascular occlusion.
- Neurologic symptoms such as vertigo and visual disturbances may occur due to hyperviscosity.
- Hypertension is often present.
- Hyperuricemia may lead to secondary gout.
- Severe pruritus, especially after a hot bath, is a common symptom.
- Erythromelalgia (burning pain in the feet or hands accompanied by erythema, pallor, or cyanosis) is common in polycythemia and is due to microvascular thrombotic occlusions.
- Congestion and plethoric appearance of the face with congested conjunctivae.
- Splenomegaly is present in polycythemia vera but absent in secondary polycythemia.
- Fundoscopy reveals congestion of the discs, engorged veins, and hemorrhages.

Investigations

- Examination of blood reveals high Hb, increased hematocrit and decreased ESR.
- Leukocyte alkaline phosphatase is high.
- The red cell volume can be accurately estimated isotopically using 51Cr labeled erythrocytes.
- Bone marrow shows hypercellularity with normoblastic hyperplasia and prominence of megakaryocytes.
- JAK2 mutation is present in virtually all patients with PV.
- Other investigations to detect the underlying cause.

Complications

- Thrombosis and hemorrhages.
- Transformation into acute myeloid leukemia, myelofibrosis or chronic myeloid leukemia.
- Cardiac failure, hypertension and secondary gout.

Treatment

- Therapy aims at keeping the blood volume normal, with the PCV around 40–45 percent.

Venesection (Phlebotomy)

- This is the mainstay of therapy in polycythemia. It is the treatment of choice in women of childbearing age and in younger patients (age <40 years). Initially about 500 ml of blood is withdrawn on alternate days to bring down the hematocrit to normal. Later on venesection can be done less frequently to maintain hematocrit below 45 percent.

Antiplatelet Agents

- Low dose aspirin (75–100 mg/day) or clopidogrel should be given to all patients with polycythemia to prevent thrombotic events. Anagrelide also inhibits platelet aggregation and can be used if other drugs are not effective.

Radioactive Phosphorus 32P

- This is a beta-emitter isotope. When administered, it is concentrated in the bone and the marrow is irradiated. Remission induced by a dose of 32P usually lasts for 2–3 years. 32P treatment is contraindicated during pregnancy.

Cytotoxic Drugs

- Drugs like busulfan, cyclophosphamide, and chlorambucil are useful in severe cases of polycythemia vera associated with high platelet count (>6 lac/mm^3), massive splenomegaly, thrombotic tendency, and elderly patients especially with poor cardiovascular status. Hydroxyurea is a safe cytotoxic drug without tumour-producing potential.

Ruxolitinib

- Ruxolitinib is an inhibitor of JAK2 pathway and is approved for the treatment of patients who donot respond to hydroxyurea.

Allopurinol

- It is useful in patients with symptomatic hyperuricemia.

Q. Differences between primary and secondary polycythemia.

6

Table 6.4 Differences between primary and secondary polycythemia

Features	Primary polycythemia (polycythemia vera)	Secondary polycythemia
Etiology	Myeloproliferative disorder	Secondary to an underlying disorder
Cell lines affected	Usually all cells lines are increased (RBCs, WBCs and platelets)	Only RBCs are increased
Erythropoietin levels	Normal or decreased	Increased
Oxygen saturation	Normal	Low
Splenomegaly	Present	Absent
Leucocyte alkaline phosphatase	Increased	Normal
Bone marrow	Panhyperplasia	Erythroid hyperplasia
Treatment	Phlebotomy, radioactive phosphorus and bone marrow suppressive agents	Mainly phlebotomy
Prognosis	Bad	Good prognosis

Q. Enumerate the causes of myelofibrosis.

Q. Discuss the etiology, clinical features, investigations and management of idiopathic myelofibrosis (primary myelofibrosis; agnogenic myeloid metaplasia).

- Myelofibrosis refers to replacement of normal bone marrow by fibrous tissue, with subsequent marked increase in extramedullary hematopoiesis (primarily in the liver and spleen, which enlarge significantly).
- Myelofibrosis can be prinmary (idiopathic) or secondary to other diseases involving bone marrow.

Causes of Myelofibrosis

Primary myelofibrosis (idiopathic)

Malignancies
- Cancer with bone marrow metastases
- Lymphoma
- Leukemias (particularly chronic myelogenous and hairy cell)
- Multiple myeloma
- Polycythemia vera
- Essential thrombocythemia
- Malignant histiocytosis
- Myelodysplastic syndrome

Toxins
- Benzene
- Thorium dioxide
- Ionizing radiation

Infections
- Tuberculosis
- Osteomyelitis

Autoimmune disorders (rarely)
- SLE
- Systemic sclerosis

Primary Myelofibrosis (Idiopathic Myelofibrosis; Agnogenic Myeloid Metaplasia)

- Primary myelofibrosis is a myeloproliferative disorder characterized by fibrosis of the bone marrow, splenomegaly, and a leukoerythroblastic peripheral blood picture with teardrop poikilocytosis.
- Fibrosis occurs due to increased secretion of platelet-derived growth factor (PDGF) and other cytokines from atypical megakaryocytes in the bone marrow.
- Since bone marrow failure occurs, compensatory extramedullary hematopoiesis takes place in the liver, spleen, and lymph nodes.

Etiology

- The exact cause of primary (idiopathic) myelofibrosis is unknown.
- It is considered to arise from a somatic mutation of a pluripotent hematopoietic progenitor cell.
- It has been linked exposure to thorium dioxide, petroleum manufacturing plants (especially toluene and benzene), and ionizing radiation.

Clinical Features

- Usually occurs over 50 years of age.
- Insidious onset.
- Fatigue and weakness due to anemia
- Weight loss due to hypermetabolic state.
- Abdominal fullness and early satiety due to splenomegaly.
- Bleeding manifestations due to due to thrombocytopenia.
- Massive splenomegaly and in some cases hepatomegaly. Painful episodes of splenic infarction may occur.
- Extramedullary hematopoiesis in the liver leads to portal hypertension with ascites, and esophageal varices.

Laboratory Findings

- Anemia is usually present.
- Total leucocyte count is variable—either low, normal, or elevated.
- The platelet count is also variable.
- *Peripheral blood smear* shows poikilocytosis and teardrop red cells. Nucleated RBCs and WBCs are present. Giant degranulated platelets may be seen. The triad of teardrop poikilocytosis, leukoerythroblastic blood, and giant abnormal platelets is highly suggestive of myelofibrosis.
- *Bone marrow*: Usually cannot be aspirated (dry tap). In early stages it is hypercellular with a marked increase in megakaryocytes and reticulin fibers. In later stages, biopsy shows severe fibrosis, with eventual replacement of hematopoietic precursors by collagen.
- Leukocyte alkaline phosphatase (LAP) score is elevated.

Treatment

- Patients with mild disease have excellent survival rate and require no specific therapy other than occasional blood transfusions.
- For younger patients with advanced disease allogeneic bone marrow transplantation is the treatment of choice.
- If bone marrow transplantation is not possible, supportive treatment with thalidomide (improves systemic symptoms, anemia, splenomegaly, and refractory cytopenias), blood transfusions and erythropoietin (for anemia), and hydroxyurea (for splenomegaly, thrombocytosis, and leukocytosis) can be used. Etanercept also improves systemic symptoms.
- Splenectomy is indicated for splenic enlargement causing recurrent painful episodes, severe thrombocytopenia, or an unacceptable transfusion requirement.
- Inhibitors of the JAK2 pathway such as ruxolitinib have a significant effect on splenomegaly and symptoms even if there is no JAK2 mutation.

Course and Prognosis

- The median survival from time of diagnosis is approximately 5 years. Newer therapies have improved survival.

Q. Essential thrombocytosis (essential thrombocythemia).

- Essential thrombocytosis is a myeloproliferative disorder characterized by marked proliferation of megakaryocytes in the bone marrow leading to increased platelet count.
- It is an uncommon disorder and the cause is unknown.

Clinical Features

- The median age at presentation is 50–60 years, and there is a slightly increased incidence in women.
- Patients may be asymptomatic and the disorder is often suspected when an elevated platelet count is found.
- Patients may present with thrombosis. Venous thromboses may occur in unusual sites such as the mesenteric, hepatic, or portal vein.
- Vasomotor symptoms such as headache, lightheadedness and erythromelalgia may be experienced by patients. Erythromelalgia is painful burning of the hands accompanied by erythema which responds to aspirin.
- Paradoxically, bleeding may occur due to qualitative platelet defect.
- Splenomegaly is present in some patients.

Laboratory Findings

- Platelet count is elevated and is usually more than 600,000/μl.
- The white blood cell count is often mildly elevated.
- Hemoglobin and RBC morphology is normal.
- Peripheral blood smear shows large and increased platelets.
- Bone marrow shows megakaryocytic hyperplasia.

Treatment

- The risk of thrombosis can be reduced by control of the platelet count, which should be kept below 500,000/μl. The drug of choice to achieve this is *hydroxyurea*. *Anagrelide* is an alternative.
- Vasomotor symptoms such as erythromelalgia and paresthesias can be controlled by aspirin.
- Daily aspirin intake reduces the risk of thrombosis.

Course and Prognosis

- Essential thrombocytosis is an indolent disorder and long-term survival is excellent. There is a small risk of transformation into myelofibrosis or acute leukemia.

Q. Myelodysplastic syndromes.

- Myelodysplastic syndrome (MDS) is group of disorders characterized by peripheral cytopenia, dysplastic hematopoietic progenitors, a hypercellular bone marrow, and a high risk of conversion to acute myelogenous leukemia (AML).
- They were also called "preleukemia" in the past since they may evolve into AML.

Etiology

- These disorders are usually idiopathic but may arise after radiation exposure and chemotherapy. Some chromosomal abnormalities such as deletions of long arms of chromosomes 5 and 7 may be seen.

Pathology

- MDS is characterized by clonal proliferation of hematopoietic cells, including erythroid, myeloid, and megakaryocytic forms. The bone marrow is normal or hypercellular, but ineffective hematopoiesis causes anemia (most common), neutropenia, and thrombocytopenia. Ineffective hematopoiesis is also associated with morphologic cellular abnormalities in bone marrow and blood. Extramedullary hematopoiesis may occur, leading to hepatomegaly and splenomegaly.
- MDS can lead to myelofibrosis or may progress to AML.

Classification

Table 6.5 French-American-British (FAB classification) of MDS

Class	Criteria
RA: Refractory anemia	Anemia with reticulocytopenia Normal or hypercellular marrow with erythroid hyperplasia and dyserythropoiesis ≤5% of blasts in bone marrow
RARS: Refractory anemia with ringed sideroblasts	Same as above with >15% ringed sideroblasts.
RAEB: Refractory anemia with excess blasts	Some cytopenia of more than two cell lines with 5 to 20% bone marrow blasts and <5% blasts in peripheral blood
RAEB-T: Refractory anemia with excess blasts in transformation	Refractory anemia with excess blasts and ≥1 of the following: • ≥5% blasts in blood • 20–30% blasts in marrow • Auer rods in granulocyte precursors
CMML: Chronic myelomonocytic leukemia	Same as refractory anemia with excess blasts and absolute monocytosis in blood Significant increase in marrow monocyte precursors

Clinical Features

- Patients are usually over 60 years of age.
- Many patients are asymptomatic, and the condition is first suspected because of abnormal blood counts.
- Patients usually present with fatigue (due to anemia), infection (due to leukopenia), or bleeding (due to thrombocytopenia) related to bone marrow failure. The course may be indolent, and the disease may present as a wasting illness with fever, weight loss, and general debility.
- Examination reveals pallor, bleeding, and signs of infection. Splenomegaly may be present.

Laboratory Findings

- Anemia may be severe and require blood transfusion.
- *Peripheral smear*: White cell count is usually normal or reduced, and neutropenia is common. The neutrophils may exhibit morphologic abnormalities, including deficient numbers of granules or a bilobed nucleus (Pelger-Huët anomaly). Promyelocytes or blasts may be seen. The platelet count is normal or reduced.
- *Bone marrow* is characteristically hypercellular, but may be hypocellular. Erythroid hyperplasia is common. Prussian blue stain may demonstrate ringed sideroblasts. The myeloid series is often left-shifted, with increased blasts.

Treatment

- Anemia is treated by red blood cell transfusions. Erythropoietin injection given weekly subcutaneously reduces the red cell transfusion requirement. Myeloid growth factors and erythropoietin can be used in combination for a better response but the cost becomes high.
- Myeloid growth factors such as G-CSF (granulocyte colony stimulating factor) help patients with severe neutropenia.
- Azacytidine (5-azacytidine) relieves symptoms, decreases the rate of transformation to leukemia and the need for transfusions, and improves survival.
- Stem cell transplantation is the only curative therapy for myelodysplasia.

Course and Prognosis

- Myelodysplasia is an ultimately fatal disease, and patients most commonly succumb to infections or bleeding.
- Patients with excess blasts have short survivals (usually <2 years) and have a higher risk of developing acute leukemia.

Q. Define lymphomas.

Q. Disuss the classification, clinical features, clinical staging, investigations and management of Hodgkin's lymphoma.

- Lymphomas are malignant transformations of lymphoid cells. They are divided into two major types: non-Hodgkin's lymphoma (NHL) and Hodgkin lymphoma (HL). NHL is the most common type of lymphoma.

Hodgkin's Lymphoma

- Hodgkin's lymphoma is named after the British physician who first described it. The cancer cells in Hodgkin's lympoma are known as Reed-Sternberg cells (named after the physicians who discovered them) which are derived from B-lymphocytes.

Etiology

- Exact cause is unknown, but genetic susceptibility; occupation such as woodworking; history of treatment with phenytoin, radiation therapy, chemotherapy; infection with Epstein-Barr virus, *Mycobacterium tuberculosis*, herpesvirus type 6, and HIV play a role.
- Immunosuppressed state (e.g. post-transplant patients taking immunosuppressants, congenital immunodeficiency disorders) also increases the risk of developing Hodgkin's lymphoma.

Pathological Classification

- Pathologically Hodgkin's lymphoma is divided into 4 subtypes:

Type	Incidence	Prognosis
Lymphocytic predominant	5%	Very good
Mixed cellularity	20%	Good
Nodular sclerosis	70%	Fair
Lymphocyte depleted	Rare	Poor

- Nodular sclerosis is the most common type and lymphocyte depleted is the least common type.

Clinical Features

- Hodgkin's lymphoma has bimodal age distribution, with one peak in the 20s and a second over age 50 years..
- More common in males.
- The majority of patients present with overt disease, most often as an asymptomatic enlarged lymph node or a mass on chest X-ray.
- Lymphadenopathy is most often found in neck. Other sites of lymh node involvement are cervical, supraclavicular, axillary, inguinal, mediastinal and intra-abdominal nodes. Involved lymph nodes are painless and nontender with a rubbery consistency.
- Constitutional symptoms such as fever in excess of 38°C, drenching night sweats, and weight loss exceeding 10 percent of baseline body weight during the 6 months preceding diagnosis are designated as symptomatic "B" disease. Fever is usually of low grade and irregular. Rarely, a cyclic pattern of high fevers for 1 to 2 weeks alternating with afebrile periods of similar duration is present at diagnosis. This fever pattern is called *Pel-Ebstein fever* and is virtually diagnostic of Hodgkin's lymphoma.
- Compression of various structures by tumor masses can producé many signs and symptoms. These are jaundice due to to bile duct obstruction, leg swelling due to lymphatic obstruction in the pelvis or groin, dyspnea due to tracheobronchial compression, paraplegia due to compression of the spinal cord, Horner syndrome due to compression of cervical sympathetic chain by enlarged lymph nodes, hoarseness of voice due to compression of recurrent laryngeal nerves, radicular pain due to compression of nerve roots, superior vena cava obstruction due to compression by enlarged mediastinal lymph nodes, etc.
- Hepatosplenomegaly may be present.
- An unusual symptom of Hodgkin's disease is pain in an involved lymph node following alcohol ingestion.
- Patients may have a variety of nonspecific symptoms reflecting organ involvement or paraneoplastic syndromes.
- Skin manifestations such as ichthyosis, urticaria, erythema multiforme, and skin infiltration, etc. may be seen.

Staging of Hodgkin's Lymphoma

- Based on the extent of the disease, it can be staged as follows (Ann Arbor staging):

Stage I: One lymph node region involved
Stage II: Involvement of two or more lymph node areas on one side of the diaphragm
Stage III: Lymph node regions involved on both sides of the diaphragm
Stage IV: Extranodal involvement (bone marrow, lungs, liver)

- In addition, patients are designated as stage A if they lack constitutional symptoms and stage B if they have constitutional symptoms (>10% weight loss over 6 months, fever, or night sweats are present).

Investigations

- Complete blood count shows normocytic normochromic anemia, normal WBC count and elevated ESR. Lymphopenia, if present is a bad prognostic factor.
- ALP may be elevated due to liver or bone involvement.
- LDH levels may be raised and indicate bad prognosis.
- Liver function tests may be abnormal due to hepatic infiltration. An obstructive pattern may be caused by enlarged nodes at the porta hepatis.
- *Chest X-ray* can show mediastinal widening due to involvement of mediastinum and lymph nodes. It can also show pericardial effusion.

- *CT scan of the thorax, abdomen, and pelvis*: This is used to establish the extent of disease.
- *Whole-body positron emission tomography (PET scan)* is more sensitive imaging technique than CT scan to find out the extent and staging of disease. PET scan can differentiate malignant from non-malignant lesions.
- *Lymph node biopsy*: It can establish the diagnosis of lymphoma. Presence of Reed-Sternberg cells is characteristic of Hodgkin's lymphoma.
- Bone marrow biopsy is required sometimes, if infiltration to bone marrow is suspected.
- Staging laparotomy is less commonly done now due to the availability of PET scan.

Treatment

Radiotherapy

- Radiotherapy is used as initial treatment only for patients with low-risk stage IA and IIA disease. Radiotherapy is also indicated for lesions causing serious pressure problems.

Chemotherapy

- Limited chemotherapy can be given for some patients treated with radiotherapy.
- Most patients with Hodgkin's disease (including stage III-B and IV disease) are best treated with combination chemotherapy using doxorubicin (adriamycin), bleomycin, vincristine, and dacarbazine (ABVD). Another regimen includes cyclophosphamide, vincristine, procarbazine, and prednisolone (COPP). These drugs are given every 3 to 4 weeks for a total of 6–8 cycles. Treatment response is assessed clinically and by repeat CT.

Autologous Stem Cell Transplantation

- Should be considered for patients who relapse after initial chemotherapy.

Combined Modality Treatment

- Radiotherapy is given after chemotherapy to sites where there was originally bulk disease.

Prognosis

- The prognosis of patients with stage IA or IIA is excellent, with 10-year survival rates in excess of 80%. Patients with disseminated disease (IIIB, IV) have poorer prognosis.

Q. Reed-Sternberg cells.

- These are the histologic hallmark of Hodgkin's lymphoma (HL). The presence of these cells differentiates Hodgkin's from non-Hodgkin's lymphoma.
- These are large malignant lymphoid cells of B cell origin with paired, mirror imaged nuclei (binucleate) with large nucleoli. There is a characteristic clear area around the nucleoli giving an "owl's eyes" appearance to the nuclei.
- They are often only present in small numbers but are surrounded by large numbers of reactive normal T cells, plasma cells and eosinophils.

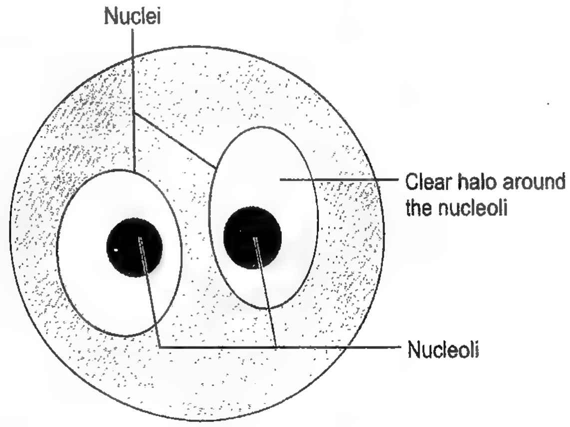

Fig. 6.5: Reed-Sternberg cells

Q. Disuss the classification, clinical features, clinical staging, investigations and management of non-Hodgkin's lymphoma (NHL).

- The non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of cancers of lymphocytes. NHL is more common than Hodgkin's lymphoma.

Classification

WHO classification of the non-Hodgkin's lymphomas

Precursor B
- B cell lymphoblastic lymphoma

Mature B
- Diffuse large B cell lymphoma
- Mediastinal large B cell lymphoma
- Follicular lymphoma
- Small lymphocytic lymphoma
- Lymphoplasmacytic lymphoma
- Mantle cell lymphoma
- Burkitt's lymphoma
- Marginal zone lymphoma (MALT type, nodal, splenic)
- Mucosal tissue associated

Precursor T
- T cell lymphoblastic lymphoma

Mature T (and NK cell)
- Anaplastic T cell lymphoma
- Peripheral T cell lymphoma

Etiology

- The exact etiology is unknown in most of the cases. Many risk factors have been identified which are as follows.

Immune deficiency states
- AIDS
- Ataxia-telangiectasia
- Immunosuppressive therapy

Occupational and environmental exposure
- Organic solvents
- Hair dyes
- Ultraviolet rays

Infectious agents
- EBV
- HTLV-1
- HHV-8
- Hepatitis-C
- *H. pylori* (gastric lymphoma)

Pathology

- Most (80 to 85%) NHL arise from B cells; the remainder arise from T cells or natural killer cells. Either precursor or mature cells may be involved.
- In most cases of non-Hodgkin's lymphoma, activation of proto-oncogenes is the major abnormality. In some cases, there may be deletion of tumor suppressor genes. For example, in Burkitt's lymphoma, there is translocation between the long arms of chromosomes 8 and 14 which causes overexpression of proto-oncogene c-*myc* which in turn leads to malignant transformation of lymphocytes. In the follicular lymphomas, the t(14,18) translocation results in overexpression of *bcl-2*, resulting in decreased apoptosis and malignant transformation.

Clinical Features

- NHL is more common in men than women.
- Its incidence increases with age and is higher in whites than in other ethnic groups. Median age 65–70 years.
- Clinical presentation can be indolent to aggressive. Patients with indolent lymphomas usually present with painless enlargement in one or more of the lymph nodes, particularly in the neck, axilla, or inguinal areas. Lymph nodes in the thorax, abdomen and pelvis can be involved. Even the indolent lymphomas are usually disseminated at the time of diagnosis, and bone marrow involvement is common.
- Patients with intermediate and high-grade lymphomas may have constitutional symptoms such as fever, drenching night sweats, or weight loss (B-symptoms). Patients with Burkitt's lymphoma may complain of abdominal pain or fullness due to frequent involvement of nodes in the abdomen.
- NHL can involve any organ in the body, and there may be clinical features relating to that organ dysfunction. Examples are neurological symptoms with CNS lymphoma, breathlessness with MALT lymphomas in the lung, epigastric pain and vomiting with gastric MALT or diffuse large B cell lymphomas, bowel obstruction with small bowel lymphomas, testicular masses with testicular lymphoma, and skin lesions with cutaneous lymphomas. SVC obstruction can occur due to mediastinal lymphadenopathy. Bone marrow involvement leads to bone marrow failure manifesting as recurrent infections, bleeding, and anemia.
- Examination reveals lymphadenopathy which is rubbery and non-tender. Hepatosplenomegaly may be present.

Investigations

- Anemia is usually present.
- ESR is raised.
- Serum LDH is usually elevated.
- Chest X-ray may show a mediastinal mass due to lymph node enlargement.
- CT scan of the chest, abdomen, and pelvis, blood tests, bone marrow biopsy, and PET scan.
- Peripheral smear is usually normal.
- Bome marrow aspiration and biopsy.
- CSF cytology if CNS involvement is suspected.
- Lymph node or tissue biopsy to confirm the diagnosis.
- Immunophenotyping of surface antigens to distinguish T and B cell tumors. This may be done on blood, marrow or nodal material.
- Genetic studies will help to find the molecular abnormality.

Treatment

- Treatment depends on whether the behavior of many of these neoplasms is indolent or aggressive, localized or disseminated and the patient condition. Some lymphomas can be managed initially with observation, whereas other situations, such as spinal cord compression require emergency treatment.

Radiotherapy

- Local radiotherapy can be used for localized low-grade lymphomas either alone or in combination with chemotherapy. Radiotherapy is also used as palliative therapy to treat symptomatic sites of relapse.

Chemotherapy

- Most patients require chemotherapy, either single or combinations of drugs. Common chemotherapy regimens include fludarabine; the combination of cyclophosphamide, vincristine, and prednisolone (R-CVP); and

cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP). Combination chemotherapy is especially helpful in intermediate and high-grade lymphomas.

Monoclonal Antibody Therapy

- Monoclonal antibodies can be used to target surface antigens on tumor cells, and induce tumor cell apoptosis. The anti-CD20 antibody rituximab has been shown to induce durable clinical responses. Synergistic effects are seen when rituximab is combined with chemotherapy.

Autologous Stem Cell Transplantation

- Individuals with very high-risk lymphoma are best treated with stem cell transplantation.

Splenectomy

- Can improve cytopenias
- Palliative therapy for symptomatic splenomegaly.

Q. Enumerate the differences between Hodgkin's and non-Hodgkin's lymphoma.

Table 6.6 Differences between HL and NHL

Feature	Hodgkin's lymphoma	Non-Hodgkin's lymphoma
Peak incidence	Bimodal peak, one peak in the 20s and another peak over age 50 years.	65–70 years
Reed-Sternberg cells	Present and pathognomonic	Absent
B-symptoms	More common	Less common
Alcohol-induced pain in involved lymph nodes	Yes	No
Dissemination at presentation	Well localized	Widespread
Origin	B lymphocytes and unifocal	B or T cells and multifocal
Involvement of extralymphatic organs	Late	Early
Involvement of Waldeyer's ring	Uncommon	Common
Involvement of epitrochlear node	Uncommon	Common
Involvement of mediastinum	Common	Uncommon
Involvement of bone marrow	Late	Early

Q. Burkitt lymphoma.

- Burkitt's lymphoma is a highly aggressive B cell non-Hodgkin's lymphoma (NHL).
- It often presents with extranodal disease and occurs most often in children and immunocompromised hosts.
- Epstein-Barr virus has been implicated in the causation of disease.

Pathology

- Most cases are associated with t(8:14), translocation between chromosomes 8 and 14.
- Burkitt's lymphoma is the most rapidly growing human tumor, and pathology reveals a high mitotic rate, a monoclonal proliferation of B cells, and a "starry-sky" pattern of benign macrophages that have engulfed apoptotic malignant lymphocytes.

Clinical Features

- Three clinical forms of Burkitt's lymphoma can be recognized: Endemic, sporadic, and immunodeficiency-associated.
- The endemic form presents as a jaw or facial bone tumor that spreads to extranodal sites.
- The nonendemic form has an abdominal presentation, with massive disease and ascites.
- Immunodeficiency-related cases more often involve lymph nodes.

Investigations

- Histology shows tumor cells, frequent mitotic figures and starry sky appearance.
- Chromosome analysis may show 8/14 translocation.
- Antibodies against EBV may be detected.

Treatment

- Treatment should be initiated within 48 hours of diagnosis.
- Combination chemotherapy CHOP (cyclophosphamide, hydroxydoxorubicin, oncovin, and prednisolone) or CODOX-M/IVAC (cyclophosphamide, oncovin, doxorubicin, methotrexate and ifosfamide, etoposide, VP-16 or etoposide, cytarabine).
- Intrathecal methotrexate for meningeal prophylaxis.

Q. Mycosis fungoides.

- Mycosis fungoides is type of non-Hodgkin's lymphoma of T cell origin with primary involvement of the skin.

Clinical Features

- It presents as a cutaneous eruption with erythematous scaly patches or plaques, often resembling eczema or psoriasis. As the disease progresses, patches may evolve into infiltrated plaques with a more generalized distribution.

Diagnosis

- Skin biopsy.
- For staging, bone marrow biopsy and CT of chest, abdomen, and pelvis.

Treatment

- Topical application of steroid, retinoid, or chemotherapeutic agents (nitrogen mustard). Other skin-directed therapies include phototherapy (UVB or PUVA, *see* below), or radiation therapy (localized electron beam therapy).

Q. Hematopoietic stem cells.

- Hematopoietic stem cells (HSCs) are the blood cells that give rise to all the other blood cells.

Sources of Hematopoietic Stem Cells

- *Bone marrow*: Marrow is the original source of stem cells. They are removed by bone marrow puncture.
- *Peripheral blood*: This has become a preferred alternative to marrow to obtain stem cells. Stem cells have to be mobilized into the peripheral blood by injecting granulocyte-macrophage colony-stimulating factor (GM-CSF).
- *Placental blood*: T lymphocytes in placental blood appear to be less alloreactive than T cells from adults and hence less likely to produce GVHD. Placental blood is obtained from the umbilical cord after birth.

Indications for Stem Cell Transplantation

- See bone marrow transplantation below.

Q. Bone marrow transplantation (hematopoietic stem cell transplantation).

Q. Allogenic bone marrow transplantation.

Q. Indications and complications of bone marrow transplantation.

- Bone marrow transplantation is now called hematopoietic stem cell transplantation. Hematopoietic stem cell has remarkable regenerative capacity, and can settle in the marrow space following intravenous injection.
- Transplantation of a few percent of a donor's bone marrow volume results in complete replacement of the recipient's entire lymphohematopoietic system, including red cells, granulocytes, B and T lymphocytes, and platelets, as well as cells comprising the fixed macrophage population, including Kupffer cells of the liver, pulmonary alveolar macrophages, osteoclasts, Langerhans' cells of the skin, and brain microglial cells.
- Human hematopoietic stem cells can survive freezing and thawing making it possible to remove and store a portion of the patient's own bone marrow for later reinfusion after treatment with high-dose myelotoxic therapy.

Types of Bone Marrow Transplantation

Syngeneic Transplantation

- Here the donor is identical twin. Advantages are, there is no risk of graft-versus-host disease (GVHD) and there is no risk of contamination with tumor cells as in autologous transplantation.

Allogeneic Transplantation

- Here the donor and recipient are not immunologically identical. Here the immune cells developing from the donor marrow can react against the recipient causing graft-*vs*-host disease (GVHD). Sometimes immunocompetent cells of the patient can reject the transplant. Hence, both donor and recipient should be HLA matched.

Autologous Transplantation

- Here patient's own stem cells are removed and stored for subsequent reinfusion after the patient receives high-dose myeloablative therapy. Unlike allogeneic transplantation, there is no risk of GVHD or graft rejection. However, autologous transplantation lacks a graft-versus-tumor (GVT) effect, and the autologous stem cell product can be contaminated with tumor cells which can lead to relapse.

Method of Transplantation

- Marrow is usually collected from the donor's posterior and sometimes anterior iliac crests with the donor under general or spinal anesthesia. Hematopoietic stem cells can also be obtained from peripheral blood after giving the donor hematopoietic growth factors for 4–5 days. Umbilical cord blood contains a high concentration of hematopoietic progenitor cells, and can be used for transplantation.
- The recipient should be prepared before transplantation which involves eradication of patient's underlying disease and, immunosuppressing the patient adequately

to prevent rejection of the transplanted marrow. However, if the donor is a histocompatible sibling, no treatment is required because no host cells require eradication. Eradication of host immune cells involves various regimens of busulfan, cyclophosphamide, melphalan, thiotepa, carmustine, etoposide, and total-body irradiation in various combinations.

- Typically, 10 to 15 ml/kg of marrow is aspirated, placed in heparinized media, and filtered to remove fat and bony spicules. Then, this marrow is infused through a large-bore central venous catheter. Cells produced by transplanted stem cells begin to appear after a week in the peripheral blood.

Indications for Bone Marrow Transplantation

Nonmalignant diseases
- Immunodeficiency disorders (severe combined immunodeficiency, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome)
- Aplastic anemia
- Hemoglobinopathies (thalassemia major)
- Storage diseases caused by enzymatic deficiencies (Gaucher's disease, Hurler's syndrome

Malignant diseases
- Acute leukemia
- Chronic leukemia
- Myelodysplasia
- Lymphoma
- Myeloma

Complications of Bone Marrow Transplantation

- *Due to preparatory regimens*: Infections due to immunosupression (herpes simplex virus, cytomegalovirus, varicella-zoster virus); cardiotoxicity; hemorrhagic cystitis if high dose cyclophosphamide is used; hair loss; and pancytopena.
- GVHD (graft-versus-host disease).
- Veno-occlusive disease of the liver.
- Graft failure.

Q. Graft-versus-host disease (GVHD).

- This is seen in allogenic bone marrow transplantation. It is the result of donor T cells reacting with host cells.
- GVHD developing within the first 3 months post-transplant is termed acute GVHD, while GVHD developing or persisting beyond 3 months post-transplant is termed chronic GVHD.
- Acute GVHD is characterized by an erythematous maculopapular rash; persistent anorexia or diarrhea, or both; and liver impairement with increased levels of bilirubin, alanine and aspartate aminotransferase, and alkaline phosphatase. Since many conditions can mimic acute GVHD, diagnosis usually requires skin, liver, or endoscopic biopsy for confirmation. In all these organs, endothelial damage and lymphocytic infiltrates are seen. The incidence of acute GVHD is higher in recipients of stem cells from mismatched or unrelated donors and in older patients.
- Chronic GVHD resembles an autoimmune disorder with malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, and bile duct degeneration and cholestasis.
- GVHD can be prevented by giving immunosuppressive drugs after transplantation. Combinations of methotrexate plus cyclosporine or tacrolimus are commonly used for this purpose. Prednisolone, anti-T cell antibodies, mycophenolate mofetil, and other immunosuppressive are also being studied. GVHD can also be prevented by removing T cells from the stem cells before transplantation but this is associated with an increased incidence of graft failure and tumor recurrence.
- GVHD can be treated with glucocorticoids, antithymocyte globulin, or monoclonal antibodies targeted against T cells.

Q. What are plasma cell disorders? Enumerate plasma cell disorders.

- Plasma cell disorders are a group of neoplastic or potentially neoplastic diseases associated with proliferation of a single clone of plasma cells derived from B cells. This group of disorders has been referred to as monoclonal gammopathies, immunoglobulinopathies, paraproteinemias, and dysproteinemias.

Classification of Plasma Cell Disorders

- Monoclonal gammopathies of undetermined significance (MGUS)
- Malignant monoclonal gammopathies (multiple myeloma, Waldenström's macroglobulinemia)
- Heavy-chain diseases
- Cryoglobulinemia
- Primary amyloidosis

Q. Discuss the etiology, clinical features, investigations and management of multiple myeloma.

- Multiple myeloma is a malignancy of plasma cells.
- It is characterized by neoplastic proliferation of a single clone of plasma cells in the bone marrow resulting in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures.

Clinical Features

- Myeloma is a disease of older adults (median age at presentation, 65 years).
- Myeloma causes clinical symptoms and signs through a variety of mechanisms.
- Replacement of the bone marrow by malignant plasma cells leads to anemia initially and later pancytopenia.
- Bone involvement causes bone pain, osteoporosis, lytic lesions, pathologic fractures, and hypercalcemia. Bone pain is most common in the back or ribs.
- Neutropenia due to bone marrow failure may lead to recurrent infections.
- Low platelet count may lead to bleeding tendency.
- The paraproteins secreted by the malignant plasma cells (either IgG or IgA) may cause hyperviscosity manifesting as vertigo, nausea, visual disturbances, and alterations in mental status.
- The light chain component of the immunoglobulin may cause renal failure. Light chain components may be deposited in various organs as amyloid causing variety of symptoms due to organ damage.
- Examination may reveal pallor, bone tenderness, and soft tissue masses. Fever may be present due to infection. Neurologic signs related to neuropathy and spinal cord compression may be present. Features of amyloidosis such as enlarged tongue, neuropathy, congestive heart failure, or hepatomegaly may be present.

Laboratory Features

- Normocytic anemia.
- Leucocyte count and platelet counts are usually normal initially but may be low with advanced disease.
- ESR is elevated due to increased rouleaux formation.
- Hypercalcemia, high uric acid and renal failure.
- The hallmark of myeloma is the finding of a paraprotein on serum protein electrophoresis. In sporadic cases, no paraprotein is present ("nonsecretory myeloma").
- Bone marrow examination shows infiltration by morphologically abnormal plasma cells.
- X-rays of bones may show multiple punched out (lytic) lesions. Such lesions are commonly seen in the axial skeleton: Skull, spine, proximal long bones, and ribs. Sometimes only generalized osteoporosis may be seen.
- Positron emission tomography (PET) scans are useful for staging of myeloma.
- Beta-2 (β_2) microglobulin level has prognostic significance in myeloma. Beta-2 microglobulin level of >4 mg/L is associated with poor prognosis.
- Bone marrow cytogenetic characteristics also have prognostic significance. Deletions of chromosome 13q and the translocation t(4,14) are associated with a poor outcome.

Treatment

- Asymptomatic patients with minimal disease can be observed without treatment since there is no advantage to early treatment of asymptomatic myeloma.
- Symptomatic patients may be treated with an initial regimen of thalidomide plus dexamethasone. Newer agents such as bortezomib and lenalidomide have improved the otcome.
- Bone marrow transplantation should be considered in young patients.
- Localized radiotherapy can reduce bone pain and eradicate the tumor at the site of pathologic fracture.
- Hypercalcemia can be treated with mobilization and hydration. The bisphosphonates (pamidronate 90 mg or zoledronic acid 4 mg intravenously monthly) reduce hypercalcemia and pathologic fractures.
- Blood transfusion for anemia.

Indicators of Poor Prognosis in Multiple Myeloma

- Low serum albumin
- Presence of renal failure
- Thrombocytopenia
- Age ≥70 years
- Advanced lytic bone leisons
- Beta-2-microglobulin >4 mg/L
- Hypercalcemia
- Low hemoglobin
- Bone marrow plasma cell percentage ≥50 percent

Q. Causes of renal failure in multiple myeloma.

- Myeloma cast nephropathy (myeloma kidney) (most common cause)
- Development of renal amyloidosis
- Renal tubular dysfunction
- Urate nephropathy due to high uric acid levels
- Recurrent urinary tract infections
- Hypercalcemia, with or without nephrocalcinosis
- Tubulointerstitial nephritis
- Plasma cell infiltration of the kidneys
- Hyperviscosity syndrome

Q. Monoclonal gammopathy of undetermined significance (MGUS).

- Monoclonal gammopathy of undetermined significance (MGUS) is the production of M-protein by noncancerous plasma cells in the absence of other manifestations typical of multiple myeloma.
- MGUS is defined by the following three criteria:
  1. Presence of a serum monoclonal protein (M-protein, whether IgA, IgG, or IgM).

2. Fewer than 10 percent plasma cells in the bone marrow
3. Absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the plasma cell proliferative process

- It is usually asymptomatic. Incidence is higher in patients over age 70.
- Diagnosis is usually suspected when M-protein is incidentally detected in blood or urine during a routine examination. MGUS is differentiated from other plasma cell disorders because M-protein levels remain relatively stable over time and lytic bone lesions, anemia, and renal dysfunction are absent.
- Although MGUS is a benign disorder, some cases may progress to other B cell related disorders such as myeloma, amyloidosis, lymphoma, or Waldenstrom's macroglobulinemia.
- Treatment is not required, but patients should be kept on follow up. Serum protein electrophoresis should be done every year to detect the progression to multiple myeloma, etc.

Q. Dicsuss the mechanism of coagulation (hemostasis).

Q. Coagulation cascade.

Q. Anticoagulants (coagulation inhibitors).

Normal Hemostasis

- The normal hemostatic process can be divided into primary and secondary components.
- *Primary hemostasis* consists of platelet plug formation at sites of injury. It occurs within seconds of injury and is of prime importance in stopping blood loss from capillaries, small arterioles, and venules. Platelet plug attaches to vessel wall through von Willebrand factor (vWF). TXA_2 (thromboxane A_2) stimulates platelet aggregation and prostacyclin inhibits platelet aggregation.
- *Secondary hemostasis* consists of fibrin formation which involves many steps in plasma coagulation system (coagulation cascade). Secondary hemostasis requires several minutes for completion and is important to prevent bleeding in larger vessels and late bleeding occurring hours or days after the injury.
- Actually these two events do not occur separately. They occur simultaneously. As the primary hemostatic plug is being formed, plasma coagulation proteins are activated to initiate secondary hemostasis.

Coagulation Cascade

- Coagulation cascade (secondary hemostasis) involves a number of steps. Each step leads to activation of a molecule which in turn activates next molecule. Coagulation cascade can start by two independent activation pathways, the intrinsic pathway and extrinsic pathway (tissue factor-mediated). Both pathways merge at the point of factor X activation and subsequent steps are same for both.

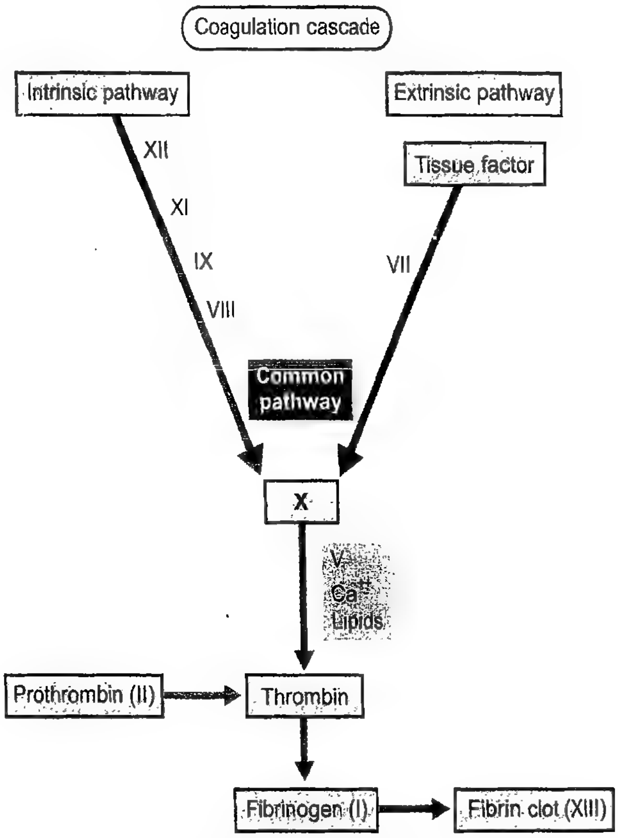

Fig. 6.6: Coagulation cascade

Anticoagulants (Coagulation Inhibitors)

- Just like there are factors which help in coagulation of blood (procoagulants), there are factors which inhibit coagulation. These are called anticoagulants. A fine balance between procoagulant and anticoagulant factors maintains the fluidity of blood.
- The flow of the blood itself inhibits coagulatiuon. Hence, blood clots when it stagnates.
- Antithrombin, proteins C and S, and TFPI (tissue factor pathway inhibitor) are important natural anticoagulant factors that maintain blood fluidity.
- These inhibitors have distinct modes of action. Antithrombin forms complexes with all serine protease coagulation factors except factor VII thus inhibiting the formation of active molecules. Protein C gets converted to activated protein C by thrombin which then inactivates factors V and VIII required for coagulation. The inhibitory function of protein C is enhanced by protein S.
- Reduced levels of antithrombin, proteins C and S, result in a hypercoagulable or prothrombotic state.

Q. Discuss the evaluation of a patient with a bleeding disorder.

Or

Q. Discuss the approach to hemorrhagic disorders.

Or

Q. How will you investigate a case of bleeding disorder?

Q. Differences between bleeding and clotting disorders.

- Bleeding results either from a breach of the vessel wall due to a specific insult (e.g. trauma) or from a defect in the hemostatic system.
- Defects in the hemostatic system may be due to a deficiency of one or more of the coagulation factors, thrombocytopenia, or occasionally excessive fibrinolysis (e.g. after fibrinolytic therapy with tPA or streptokinase).
- Detailed history and physical examination are important in finding out the cause of bleeding disorder.

History

- The following points should be elicited from the history:
- *Site of bleeds*: Superficial bleeds (skin and mucous membranes), epistaxis, gastrointestinal hemorrhage or menorrhagia indicates a platelet disorder, thrombocytopenia or von Willebrand's disease. Deep seated bleeding such as bleed into muscle, joint or retroperitoneum indicate a coagulation defect. Recurrent bleed at the same site indicates a local structural abnormality.
- *Duration of history*: Onset in childhood may suggest a coagulation defect such as hemophilia. It also suggests inherited hemostatic disorder.
- *Precipitating causes*: Bleeding arising spontaneously indicates a more severe defect than bleeding that occurs only after trauma.
- *Surgery or trauma*: Ask about all past surgeries or trauma. Bleeding from a platelet disorder usually occurs immediately after trauma or surgery, and is easily controlled by local measures (such as local pressure). Bleeding due to coagulation defects (e.g. hemophilia) occurs hours or days after injury, and cannot be controlled by local measures.
- *Family history*: A family history of bleeding suggests an inherited hemostatic disorder such as hemophilia. However, about one-third of cases of haemophilia arise in individuals without a family history.
- *Systemic illnesses*: Enquire about the presence of liver disease, renal failure, paraproteinaemia or a connective tissue disease (vasculitis) which can cause bleeding.
- *Drugs*: Many drugs can cause bleeding either by bone marrow suppression or by inhibiting vit-K dependent clotting factors and platelets. Examples are aspirin, clopidogrel, warfarin, etc.

Physical Examination

- Examination should note the presence of any bleeding in the skin and mucous membranes such as petechiae, ecchymoses and hematomas.
- Bleeding into body cavities, the retroperitoneum, or joints is common in coagulation disorders such as hemophilia.
- Joint deformities may be present in coagulation disorders due to recurrent bleeding.
- Hematomas can also compress nerves and lead to neurological deficits. For example, retroperitoneal hematoma can compress femoral nerve. Intracerebral bleed can lead to stroke and altered sensorium. Intracerebral bleed is the leading cause of death in hemostatic disorders.
- Look for evidence of liver disease; splenomegaly may cause thrombocytopenia due to hypersplenism.

Table 6.7 Investigations done in bleeding and clotting disorders

Investigation	Normal value	Significance
• Platelet count	1.5 to 4.5 lakhs	Low in many disorders. Low count causes prolongation of bleeding time whereas PT remains normal
• Bleeding time	<8 mins	Prolonged in thrombocytopenia, abnormal platelet function, and deficiency of von Willebrand's factor
• Prothrombin time (PT)	12–15 seconds	PT screens the extrinsic or tissue factor—dependent pathway. PT is prolonged in deficiencies of factors II, V, VII, and X, vitamin K deficiency, and warfarin use
• Activated partial thromboplastin time (APTT)	30–40 seconds	Screens the intrinsic limb of the coagulation system. APTT is prolonged in deficiencies of factors II, V, VIII, IX, X, XI, XII, heparin-antibodies against clotting factors and presence of lupus anticoagulant
• Fibrinogen level	1.5–4.0 g/L	Low levels found in DIC and liver disease
• Thrombin time	3–5 seconds	Tests the conversion of fibrinogen to fibrin

6

Table 6.8 Differences between primary and secondary clotting disorders

Features	Primary hemostatic disorder (bleeding disorder, e.g. platelet defects)	Secondary hemostatic disorder (coagulation disorder, e.g. hemophilia)
• Onset of bleeding after trauma	Immediate	Delayed—hours or days
• Age of onset	Late	Childhood
• Sites of bleeding	*Superficial*: Skin and mucous membranes	*Deep*: Joints, muscle, retroperitoneum
• Physical findings	Petechiae and ecchymoses	Hematomas, hemarthroses
• Family history	Usually absent	Usually present
• Inheritance	Autosomal dominant	Autosomal or X-linked recessive
• Local measures	Can control bleeding	Cannot control bleeding

Q. Causes of thrombocytopenia.

Q. Define thrombocytopenia. Discuss the causes, clinical features, investigations and management of thrombocytopenia.

Q. Tourniquet test (capillary resistance test; Hess test).

- Thrombocytopenia is defined as a platelet count less than 150,000/µl (normal 150,000 to 450,000)

Causes of Thrombocytopenia

Decreased production
- Aplastic anemia
- Marrow infiltration (leukemia, myeloma, carcinoma, myelofibrosis, osteopetrosis)
- Myelodysplasia
- Vitamin B_{12} and folic acid deficiency
- Chronic alcoholism
- Infections (rubella, mumps, varicella parvovirus)
- Drugs (cytotoxics, antimetabolites thiazides)

Increased destruction
- Idiopathic thrombocytopenic purpura
- HELLP syndrome (hemolytic anemia, elevated liver function tests, and low platelet count) in pregnant women
- Secondary (CLL and SLE)
- Hypersplenism
- Disseminated intravascular coagulation (DIC)
- Thrombotic thrombocytopenic purpura
- Hemolytic-uremic syndrome
- Sepsis
- Hemangiomas
- Infections (dengue and HIV)
- Drugs

Dilutional
- After massive blood transfusion

Clinical Features

- Bleeding manifestations may not occur until the platelet count falls below 10,000/µL.
- Patients present with bleeding manifestations from cutaneous and mucous membranes.
- Bleeding manifestations include epistaxis, petechiae, purpura, ecchymosis, GI bleed and genitourinary bleeding. Women may present with menorrhagia. Intracranial bleeding can occur in severe thrombocytopenia and cause death.
- *Tourniquet test (Hess test)*: A sphygmomanometer cuff is tied around the arm and inflated above diastolic blood pressure but below systolic pressure. Cuff is deflated after 5 minutes. In thrombocytopenia, petechial spots appear in the forearm. More than 20 petechial spots in 3 cm area is considered positive Hess test. It is due to the increased capillary fragility in thrombocytopenia.

Investigations

- Low platelet counts.
- Anemia may be present due to blood loss.
- Prolonged bleeding time.
- *Peripheral smear*: This gives information on morphology of cells, presence or absence of platelet clumping, etc. Peripheral smear can also diagnose diseases such as leukemia.
- *Bone marrow examination*: This may show aplasia, an infiltrative disease, or increased number of megakaryocytes in excessive peripheral destruction (e.g. in ITP).
- *Other tests*: Should be directed at the suspected cause. HIV serology, liver function tests, ultrasound abdomen to look for splenomegaly, etc. are helpful.

Management

- Treat the underlying cause
- Platelet transfusion is required if the platelet count is less than 20,000/cumm.

Q. Drug induced thrombocytopenia

- Many drugs can cause thrombocytopenia. Drugs may suppress bone marrow thus causing thrombocytopenia or increase peripheral destruction of platelets.

- Drugs such as NSAIDs exacerbate underlying platelet disorder.
- A detailed drug history should be elicited in all patients with thrombocytopenia. Following is the list of drugs which commonly cause thrombocytopenia.
  - Heparin
  - Valproic acid
  - Gold salts
  - Quinine
  - Trimethoprim-sulfamethoxazole and other sulfonamides
  - Interferons
  - Glycoprotein IIb/IIIa inhibitors (e.g. abciximab)
- Management involves withdrawing the offending drug.

Q. Heparin-induced thrombocytopenia (HIT).

- Heparin-induced thrombocytopenia (HIT) is the most common type of drug-induced thrombocytopenia.
- There are two types of HIT. Type 1 HIT presents within the first 2 days after exposure to heparin, and the platelet count normalizes even with continued heparin therapy. Type 1 HIT is due to the direct effect of heparin on platelet activation.
- Type 2 HIT is an immune-mediated disorder that typically occurs 4–10 days after exposure to heparin. It is caused by an IgG autoantibody that reacts with platelet factor 4 (PF4) on the platelet surface, usually in a complex with heparin. The interaction of the antibody with PF4 is prothrombotic due to the release of platelet microparticles into the circulation. Because of prothrombotic state, arterial and venous thromboses may occur. In general medical practice, the term HIT refers to type 2 HIT.
- The risk of HIT is higher with unfractionated heparin than with low-molecular-weight heparin. It is seen usually after 4 days of heparin use and often the first finding is asymptomatic thrombocytopenia.
- Finding HIT antibodies confirms the diagnosis.
- Treatment involves stopping heparin and using alternative forms of anticoagulation. The direct thrombin inhibitors such as argatroban and lepirudin can be used as alternatives to heparin.

Q. Describe the etiology, clinical features, diagnosis and management of idiopathic (autoimmune) thrombocytopenic purpura (ITP).

- Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder due to the presence of an IgG autoantibody against platelets.

Etiology

- ITP is due to development of antibodies to one's own platelets, usually triggered by a preceding infection. Any infection can trigger antibody production but common cause is viral infections.

Pathogenesis

- Antibody bound platelets are destroyed in the spleen, where splenic macrophages with Fc receptors bind to antibody-coated platelets. Since the spleen is the major site both of antibody production and platelet destruction, splenectomy is highly effective therapy for ITP.

Clinical Features

- ITP is a disease of young. Peak incidence is between ages 20 and 50 years.
- Females are more commonly affected than males.
- Patients present with mucosal or skin bleeding. Common types of bleeding are epistaxis, oral bleeding, menorrhagia, purpura, and petechiae. Intracerebral bleed can be fatal in these patients.
- On examination, patient appears well. Bleeding manifestations such as petechiae and purpura may be noted. In ITP, usually there is no splenomegaly and presence of splenomegaly should make one suspect an alternative diagnosis.

Laboratory Features

- The hallmark of the disease is thrombocytopenia. Platelet counts can be very low such as less than 10,000/µl.
- Bleeding time is prolonged due to low platelets but clotting time is normal.
- Other counts are usually normal except for occasional mild anemia due to bleeding.
- Peripheral smear is normal except reduced platelets.
- Bone marrow is normal except increased number of megakaryocytes.

Differential Diagnosis

- Thrombotic thrombocytopenic purpura
- DIC
- Gestational thrombocytopenia
- Drug induced thrombocytopenia
- Infections (e.g. dengue, HIV)
- Hypersplenism
- Myelodysplasia
- Congenital thrombocytopenias
- Acquired pure megakaryocytic aplasia

Treatment

- A few patients may have spontaneous remission, but most will require treatment.

Platelet Transfusions

- Platelet transfusions are given if the platelet count is below 20,000/µl because spontaneous bleeding can occur below this level. However, even these exogenous platelets are destroyed and the effect lasts only a few hours. Platelet transfusion should be reserved for cases of life-threatening bleeding in which even fleeting hemostasis may be of benefit.

Steroids

- Prednisolone 1–2 mg/kg/d acts by decreasing the affinity of splenic macrophages for antibody-coated platelets. It also reduces the production of antbody and binding of antibody to the platelet surface. Platelet count will usually begin to rise within a week, and responses are almost always seen within 3 weeks. Steroids are continued until the platelet count is normal, and the dose should then be gradually tapered. Dexamethasone can also be used.

Immunoglobulin Therapy

- Intravenous immunoglobulin (IVIG), 1 g/day for 3 to 5 days, is highly effective in raising the platelet count.
- IVIG works by blocking Fc receptors on macrophages, thereby inhibiting phagocytosis. However, this treatment is expensive, and it should be reserved for bleeding emergencies. A less expensive alternative is Rho immunoglobulin (RhIG) which is anti-Rh antibody. Mechanism of action is same as that of IVIG.

Splenectomy

- Splenectomy is indicated if patients do not respond to other therapies such as steroids or immunoglobulins.

Other Therapies

- These are tried if the patient does not respond to above therapies.
  - Danazol.
  - Immunosuppressive agents (vincristine, azathioprine, cyclosporine, and cyclophosphamide).
  - Rituximab.
  - High-dose immunosuppression and autologous stem cell transplantation.

Prognosis

- Prognosis is good and most patients will recover with medical line of management. Patients may die due to intracranial hemorrhage.

Q. Thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome (TTP–HUS).

- Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are acute, fulminant disorders characterized by thrombocytopenia and microangiopathic hemolytic anemia.
- Although some studies appear to distinguish between TTP and HUS, the presenting features are essentially the same in most adult patients.

Etiology

- Idiopathic
- Drugs (quinine, cyclosporine, clopidogrel)
- Autoimmune disease (SLE, scleroderma)
- Infection (enterohemorrhagic *E. coli*, O157:H7, HIV)
- Pregnancy/postpartum state
- Hematopoietic cell transplantation
- Malignancy

Pathology

- TTP and HUS involve nonimmunologic platelet destruction. Loose strands of platelets and fibrin are deposited in multiple small vessels and damage passing platelets and RBCs, causing significant thrombocytopenia and anemia. Platelets are also consumed within multiple small thrombi. Multiple organs get affected due to the formation of thrombi in microvasculature (thrombotic microangiopathy). The brain, heart, and kidneys are particularly likely to be affected.
- TTP and HUS differ mainly in the relative degree of kidney failure. TTP is less likely to involve kidneys. However, HUS typically involves kidney failure.

Clinical Features

- Clinically there is a pentad of diagnostic features:
  1. Thrombocytopenia
  2. Microangiopathic hemolytic anemia
  3. Neurologic symptoms and signs
  4. Renal function abnormalities
  5. Fever
- Renal abnormalities include hematuria and/or proteinuria
- Neurologic symptoms and signs are confusion or headache. Focal deficits are uncommon. Seizures and coma can occur.

Diagnosis

- Typical clinical features.
- Presence of thrombocytopenia and anemia.
- Presence of schistocytes in peripheral smear suggesting microangiopathic hemolytic anemia.
- Normal clotting tests.

Treatment

- Daily plasma exchange: Plasma exchange reverses the platelet consumption that is responsible for the thrombus formation in microcirculation.
- Corticosteroids can be used with plasma exchange.
- Rituximab is useful when there is reccurence after when plasma exchange is stopped or in patients with relapses.
- Eculizumab inhibits complement system and is useful in patients with HUS refractory to plasma exchange and/or corticosteroids.

Q. Discuss the etiology, clinical manifestations, investigations and management of von Willebrand's disease.

Q. von Willebrand's factor.

- von Willebrand's disease is the most common congenital bleeding disorder and is transmitted in an autosomal dominant pattern. Rarely it can be acquired also.

Etiology

- von Willebrand's disease is due to deficient or defective von Willebrand's factor (vWF).
- vWF is important for platelet adhesion to sub-endothelium. vWF is synthesized by megakaryocytes and endothelial cells. The gene for von Willebrand's factor is located on chromosome 12.
- vWF also acts as a carrier for factor VIII in the circulation, increasing the half-life of factor VIII. Hence, in von Willebrand's disease, there may be secondarily coagulation disturbance due to decreased levels of factor VIII.

Clinical Features

- von Willebrand's disease affects both men and women.
- Most cases are mild.
- Patients present with mucosal bleeding (epistaxis, gingival bleeding and menorrhagia).
- Some patients may come to attention because of excessive bleeding after surgical incisions or dental extractions. Bleeding tendency is exacerbated by aspirin.
- Characteristically, bleeding decreases during pregnancy or estrogen use.

Investigations

- Bleeding time is prolonged in the presence of normal platelet count.
- Defective or absent platelet aggregation.
- Levels of von Willebrand's factor in plasma are reduced.
- Ristocetin cofactor test is the most specific and shows decreased biological activity of vWF.

Management

- Since the bleeding is mild, no treatment is necessary except before surgery or dental procedures.
- Desmopressin acetate (DDAVP) can increase the vWF levels by two-to three-fold by releasing stored vWF from endothelial cells. It can be given before surgery or dental procedures.
- The antifibrinolytic agent ε-aminocaproic acid (EACA) is useful as adjunctive therapy during dental procedures. It is given after DDAVP.

Q. Discuss the etiology, clinical features, investigations and management of hemophilia A.

Q. Factor VIII (antihemophilic factor).

- Hemophilia-A (classic hemophilia) is a hereditary bleeding disorder due to deficiency of coagulation factor VIII.
- Most of the cases are due to quantitative reduction of factor VIII. However, a small number of cases is due to qualitative defect in factor VIII.
- Hemophilia is an X-linked recessive disease, and hence, males are usually affected. However, rarely, female carriers can be affected if their normal X chromosome is also disproportionately inactivated. Females may also become affected if their father is a hemophiliac and mother is a carrier.
- Antenatal diagnosis can be made by chorionic villous sampling or amniocentesis.

Pathogenesis

- *Factor VIII (antihemophilic factor)* is a large (265-kDa) single-chain protein that regulates the activation of factor X by proteases generated in the intrinsic pathway. Hence, deficiency of factor VIII leads to defective coagulation and bleeding.
- Factor VIII is synthesized in liver and circulates in the blood. von Willebrand's factor (vWF) acts as a carrier of factor VIII in blood.
- The gene for factor VIII is on the X chromosome, and carrier detection and prenatal diagnosis are well established. One in 10,000 males is born with deficiency or dysfunction of the factor VIII molecule.
- Hemophilia is classified as severe if factor VIII level is less than 1%, moderate if level is 1–5%, and mild if level is greater than 5%.

Clinical Features

- Hemophilia A is the second most common congenital bleeding disorder after von Willebrand's disease. It is a severe bleeding disorder.

- Family history of hemophilia is usally positive.
- The bleeding tendency is related to factor VIII levels. Patients with mild hemophilia bleed only after major trauma or surgery, those with moderately severe hemophilia bleed with mild trauma or surgery, and those with severe disease bleed spontaneously.
- Bleeding can occur anywhere but commonly occurs in deep tissues such as joints (knees, ankles, elbows), muscles, and from GIT.
- Bleeding into joints (hemarthroses) is common in hemophilia-A and is almost diagnostic of the disorder. Recurrent bleeding into joints leads to joint destruction and joint deformities.
- Earlier when HIV screening of donor blood was not widely adopted, many hemophiliacs got infected with HIV due to factor VIII transfusion and many of these have already developed AIDS. However, this is uncommon now due to universal screening of donor blood.

Investigations

- Partial thromboplastin time (PTT) is prolonged.
- Platelet count and PT are normal.
- Bleeding time and fibrinogen levels are also normal.
- Factor VIII levels are reduced.

Treatment

- Treatment of hemophilia A involves infusion of factor VIII concentrates, either recombinant or heat treated.
- In minor bleeding, it is enough if the factor VIII levels are raised to 25% of normal. For moderate bleeding, levels should be kept above 25% of normal. When major surgery is to be performed, factor VIII level should be raised to 100% and then maintained above 50% for 10–14 days.
- For mild hemophiliacs, DDAVP (desmopressin) is enough for minor surgeries. It causes release of stored factor VIII and will raise the factor VIII levels two-to threefold for several hours.
- EACA (epsilon aminocaproic acid) may be added if bleeding persists after treating with factor VIII and desmopressin.
- Fresh frozen plasma can be used if factor VII concentrate is not available.
- Gene therapy is currently in the developmental phase.
- Avoid the use of aspirin in these patients.

Prognosis

- Prognosis is good now because of the availability of factor VIII concentrates. Intracerebral hemorrhage is the usual cause of death but uncommon.

Q. Discuss the etiology, clinical features, investigations and management of hemophilia B (Christmas disease).

- Hemophilia B (Christmas disease) is a hereditary bleeding disorder due to deficiency of coagulation factor IX. It is sometimes called Christmas disease, named after Stephen Christmas, the first patient described with this disease. Inheritance is same as hemophilia A (X-linked recessive).
- Most cases are due to reduced levels of factor IX but some cases may be due to qualitative defect in factor IX.
- Factor IX deficiency is less common than factor VIII deficiency but is otherwise clinically and genetically identical.

Clinical Features

- Same as hemophilia A, but less severe.

Investigations

- Factor IX levels are reduced.
- Other laboratory features are same as factor VIII deficiency.

Treatment

- Transfusion of factor IX concentrates. Recombinant factor IX is available now.
- Fresh frozen plasma can be used in emergencies if factor IX concentrate is not available.
- DDAVP is not useful in this disorder.
- Aspirin should be avoided.

Prognosis

- Prognosis is same as hemophilia A.

Q. Classify anticoagulants. Give a brief account of commonly used anticoagulants.

Q. Indications of anticoagulation.

Q. Warfarin.

Q. Heparin.

Q. Low-molecular-weight heparins (LMWHs).

Anticoagulants are agents which interfere with coagulation of blood. They are useful in a variety of disorders associated with abnormal blood coagulation.

Classification

- *Oral*: Warfarin, phenindione, coumarin
- *Parenteral*: Unfractionated heparin and LMWH.

- *Newer anticoagulants*: Direct thrombin inhibitors (hirudin, melagatran and argatroban), activated protein C, thrombomodulin. Argatroban and hirudin are useful in heparin induced thrombocytopenia (HIT).

Uses

- Prophylaxis and treatment of deep vein thrombosis.
- Pulmonary embolism.
- Myocardial infarction.
- Atraial fibrillation.
- Patients with mecahnical prosthetic valves.

Adverse Effects

- Bleeding (monitor APTT in patients with heparin and PT in patients on warfarin)
- HIT (heparin induced thrombocytopenia with unfractionated heparin)
- Osteoporosis
- Hypersensitivity reactions

Warfarin

- Warfarin is a coumarin derivative. It inhibits vitamin K reductase thus causing depletion of reduced vit K required for the production of functionally active (gama-carboxylated) coagulation proteins (factors 7, 9, and 10) and anticoagulant proteins (protein C and protein S).
- Warfarin is well absorbed orally. It has a delayed onset of action (2 to 7 days) and half-life of about 40 hours. Its anticoagulant effect lasts for 4–5 days after discontinuation.
- The effect of warfarin is influenced by many factors, including age, liver disease, dietary vitamin K_1, genetic factors, concomitant drug use, patient compliance, and inappropriate dosage adjustments. The effect of warfarin varies widely among individuals, and hence should be monitored closely.
- Its effect can be monitored by prothrombin time and is reported as international normalized ratio (INR).

Indications for Warfarin

- Atrial fibrillation (AF).
- Valvular heart disease (native and prosthetic tissue and mechanical heart valves).
- Prevention and treatment of venous thromboembolism.
- Prevention of acute myocardial infarction (MI) in high-risk patients.
- Prevention of stroke, recurrent MI, and death in patients with acute MI.

Dosing and Monitoring

- Warfarin should be started at low dose (5 mg daily) and titrated as required. Lesser starting dose (3 – 4 mg) should be used in elderly because they are more sensitive to warfarin.
- If a rapid anticoagulant effect is required, heparin and warfarin should be started simultaneously and overlapped for at least 5 days. Then, heparin is discontinued when the INR is in the therapeutic range for 2 days.
- INR (international normalized ratio) should be monitored frequently in patients on warfarin therapy.
- A target INR of 2.5 (range 2.0 to 3.0) is recommended for all indications except for patients with mechanical prosthetic heart valves, for which an INR of 3.0 (range 2.5 to 3.5) is recommended.

Adverse Effects

- Increased risk of bleeding. Elderly patients are at higher risk of bleeding including intracranial bleeding.

Reversing the Effect of Warfarin

- The anticoagulant effect of warfarin can be reversed by stopping the drug, by administering vit K or fresh-frozen plasma. Vitamin K is a natural antagonist of warfarin.

Heparin

- Heparin acts as an anticoagulant by activating antithrombin (AT) which inactivates thrombin, factor Xa, and other coagulation enzymes. Anticoagulant effect of heparin is monitored by activated partial thromboplastin time (aPTT).

Uses

- Prevention and treatment of venous thromboembolism.
- Unstable angina and acute MI.
- Cardiopulmonary bypass.
- During and after coronary angioplasty and coronary stenting.
- During hemodialysis.

Adverse Effects

- Increased risk of bleeding.
- Heparin induced thrombocytopenia (HIT).

Low-Molecular-Weight Heparins (LMWHs)

- LMWHs are fragments produced by chemical or enzymatic depolymerization of heparin. LMWHs are approximately one-third the size of heparin.
- Examples: Enoxaparin and dalteparin.

Advantages

- They have less protein and cellular binding and, hence, have more predictable anticoagulant response, better bioavailability, and longer plasma half-life than regular heparin. LMWHs are excreted mainly by kidneys.

- LMWHs are associated with a lower incidence of heparin induced thrombocytopenia (HIT) and heparin-induced osteoporosis than heparin.
- Since LMWHs have a longer plasma half-life and a more predictable anticoagulant effect, they can be administered once daily without laboratory monitoring.

Indications

- Same as those for heparin.

Q. New oral anticoagulants.

Q. Dabigatran and Rivaroxaban.

- Vitamin K antagonists (warfarin) were the only class of oral anticoagulants available to clinicians for decades. Warfarin has many disadvantages which include long period of onset of action, unpredictable pharmacokinetics, significant interaction with food and other drugs, and the need to monitor prothrombin time regularly.
- However, now with the availability of some new oral anticoagulants, such as dabigatran, rivaroxaban, etc. clinicians have broader choice.

Dabigatran

- Dabigatran is the first oral direct thrombin inhibitor to be approved.

Mechanism of Action

- Dabigatran binds to thrombin and blocks its procoagulant activity.

Indications

- Prevention of stroke and systemic embolism in adult patients with atrial fibrillation.
- To prevent deep vein thrombosis.

Dosage

- The recommended dose is 150 mg orally twice daily.

Advantages Over Warfarin

- There is no need to monitor prothrombin time.
- Bleeding risk is less.

Side Effects

- Dyspepsia incidence is more than warfarin.
- Risk of myocardial infarction is slighltly increased.

Rivaroxaban

- Rivaroxaban is a new oral anticoagulant which acts by inhibiting factor Xa.
- Indications and advantages are same as dabigatran

Q. Discuss the etiology, clinical features, investigations and management of disseminated intravascular coagulation (DIC; comsumptive coagulopathy)

- Disseminated intravascular coagulation (DIC) involves abnormal, excessive generation of thrombin and fibrin in the circulating blood. During the process, increased platelet aggregation and consumption of coagulation factors occur.
- DIC produces both thrombosis and hemorrhage. DIC that evolves slowly (over weeks or months) causes primarily venous thrombotic and embolic manifestations; DIC that evolves rapidly (over hours or days) causes primarily bleeding.

Etiology

- DIC usually results from exposure of tissue factor to blood, initiating the coagulation cascade. DIC most often occurs in the following circumstances.
  - Sepsis
  - Crush injury
  - Severe head injury
  - Malignancy (Trousseau's syndrome)
  - Acute leukemia, especially promyelocytic
  - Complications of pregnancy (amniotic fluid embolism, HELLP syndrome, eclampsia, retained fetal products and septic abortion)
  - Amphetamine overdose
  - Giant hemangioma (Kasabach-Merritt syndrome)
  - Abdominal aortic aneurysm
  - Hemolytic transfusion reaction (ABO incompatibility)
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Snakebite
  - Fulminant hepatic failure
  - Severe burns

Pathogenesis

- Normally coagulation is mediated by thrombin and kept confined to a localized area by a combination of blood flow and coagulation inhibitors especially antithrombin III. When these mechanisms are overwhelmed by the markedly increased production of thrombin, thrombin may circulate and lead to disseminated intravascular coagulation.
- There is widespread deposition of fibrin leading to blocked blood vessels and tissue ischemia, consumption of platelets, fibrinogen, prothrombin, factors V and VIII. Consumption of all these coagulant factors in turn may lead to bleeding. The major stimulus to thrombin activation in DIC comes from the tissue factor.

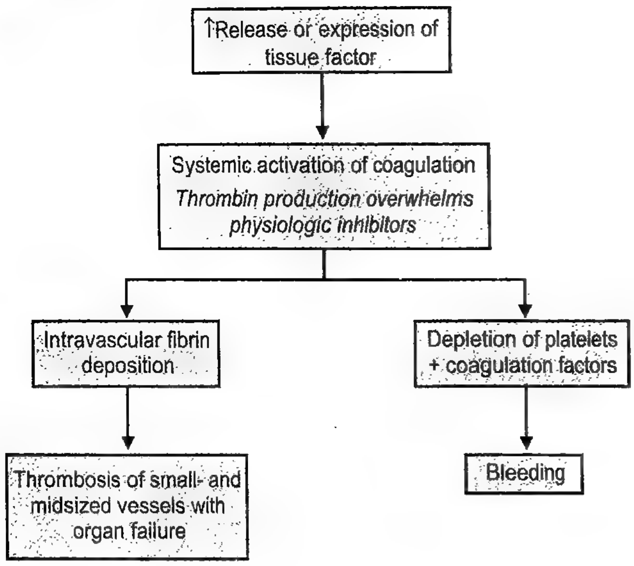

Fig. 6.7: Pathophysiology of DIC

Clinical Features

- DIC leads to both bleeding and thrombosis. Bleeding is more common than thrombosis.
- Bleeding may occur at any site, but spontaneous bleeding and oozing at venipuncture sites or wounds are important clues to the diagnosis.
- Thrombosis is most commonly manifested by digital ischemia and gangrene.
- Other manifestations include dysfunction of liver, kidney, lungs, and central nervous system. DIC also causes microangiopathic hemolytic anemia.

Laboratory Findings

- Hypofibrinogenemia, thrombocytopenia, and elevated fibrin degradation products. D-dimer is the most sensitive fibrin degradation product.
- PT is prolonged.
- APTT may or may not be prolonged.
- Peripheral smear shows fragmented RBCs due to microangiopathic hemolytic anemia.
- Antithrombin III levels may be markedly reduced.

Treatment

- Underlying cause of DIC should be treated
- *Replacement therapy*: Platelets should be transfused to maintain a platelet count greater than 30,000/μl. Fibrinogen is replaced with cryoprecipitate. Coagulation factor deficiency may require replacement with fresh-frozen plasma. When there is excessive fibrinolysis, EACA 1 g intravenously per hour may be tried in combination with heparin. EACA should not be used without heparin in DIC because of the risk of thrombosis. Antithrombin III replacement has not been shown to reduce mortality rate of severe sepsis with DIC. However, one trial has shown benefit by the use of activated protein C.
- The role of heparin in the treatment of DIC is controversial. Clearly, it is contraindicated before or after neurosurgical procedures. Heparin is useful in slowly evolving DIC which presents primarily with thrombosis. It is also useful in the presence of thrombosis or fibrin deposition leading to acral cyanosis. Hepain is usually not indicated in rapidly evolving DIC with bleeding manifestations except in women with a retained dead fetus and evolving DIC with a progressive decrease in platelets, fibrinogen, and coagulation factors. A dose of 500–750 units per hour of heparin is enough in DIC and aPTT need not be prolonged for clinical benefit. Heparin is not effective if antithrombin III levels are markedly reduced. If antithrombin III levels are very low, it can be raised by giving fresh-frozen plasma or antithrombin III concentrates.

Q. Vitamin K.

- The name "K" comes from the German/Danish word koagulations vitamin (clotting vitamin). Vitamin K plays an important role in coagulation by acting as a cofactor for the posttranslational carboxylation of coagulation factors II, VII, IX, and X. Without carboxylation, coagulation reactions occur slowly and hemostasis is impaired.
- Vitamin K is primarily supplied by diet (green vegetables like spinach and broccoli) and syntheisis by intestinal bacteria.
- Vitamin K is a fat soluble vitamin. Pancreatic and biliary function need to be intact for proper vitamin K absorption. Dietary vitamin K is protein-bound and requires pancreatic enzymes in the small intestine for liberation. Bile salts then solubilize vitamin K into luminal micelles for absorption.
- Deficiency develops because of inadequate diet, use of broad-spectrum antibiotics, liver and pancreatic disorders. A patient not taking orally and is put on broad-spectrum antibiotics can develop vit K deficiency in as little as 1 week.

Clinical Features

- There are no specific clinical features. Bleeding can occur at any site. Vitamin K deficiency is common in the newborn and can manifest as hemorrhagic disease of the newborn. Hence, parenteral vit K is given routinely to newborns.

Laboratory Findings

- In mild vitamin K deficiency only the PT is prolonged.
- In severe vitamin K deficiency both PT and PTT are prolonged, but PT is more prolonged than aPTT.

Treatment

- Vitamin K should be replaced parenterally either subcutaneously or intravenously. A single dose of 15 mg will completely correct laboratory abnormalities in 12–24 hours.

Q. Antiphospholipid syndrome (antiphospholipid antibody syndrome.

- The antiphospholipid syndrome (APS) also known as antiphospholipid antibody (APLA) syndrome is characterized by antibodies directed against either phospholipids or plasma proteins bound to anionic phospholipids.
- These antiphospholipid antibodies include lupus anticoagulant ((also known as lupus antibody) and anticardiolipin (aCL) antibody. The antibodies in APS have prothrombotic effect and also have action on vascular tone causing the clinical manifestations of APS.

Etiology

- APS is an autoimmune disorder of unknown cause. However following conditions can be associated with APS.
- *Autoimmune diseases*: SLE, Sjögren syndrome, Rheumatoid arthritis.
- *Infections*: Syphilis, hepatitis C infection and HIV infection
- *Drugs*: Procainamide, quinidine, propranolol, hydralazine, phenytoin and chlorpromazine.
- *Genetic predisposition*: Relatives of persons with known APS are more likely to have APS.
- *HLA associations*: Individuals who carry certain HLA genes *DR7* and *DR4 have increased risk of developing APS.*

Clinical Features

- These patients may have a variety of clinical manifestations including venous and arterial thrombosis, recurrent fetal losses, neurologic events, and thrombocytopenia.
- *Thrombotic events*: Deep vein thrombosis and pulmonary embolism, ischemic stroke, peripheral and intra-abdominal vascular occlusion.
- *Obstetric complications*: Recurrent spontaneous abortions and fetal growth retardation, which probably are due to thrombosis of placental vessels.

Diagnosis

- Diagnosis of antiphospholipid syndrome is based on a combination of clinical history and laboratory testing. Presence of lupus anticoagulant and anticardiolipin antibodies should be tested.

Treatment

Prophylactic Therapy to Prevent Thrombosis

- Prophylaxis is needed during surgery or hospitalization. Low-dose aspirin or clopidogrel can be used to prevent thrombotic events.

Patients with History of Thrombosis

- Intravenous heparin followed by warfarin should be used. International normalized ratio (INR) should be maintained between 2 and 3. Lifelong treatment may be required for patients with recurrent thrombotic events.

Pregnant Women with APS

- Treatment of antiphospholipid syndrome during pregnancy reduces the risks of pregnancy loss, pre-eclampsia, placental insufficiency, preterm birth, and thrombosis. Women with antiphospholipid syndrome and no history of thrombosis should receive heparin and low-dose aspirin during pregnancy and for six to eight weeks postpartum. Patients who require heparin administration throughout pregnancy should receive calcium and vitamin D supplementation to help avoid heparin-induced osteoporosis.
- Some studies have shown that aspirin alone is as efficacious as heparin plus aspirin.

Q. Lupus anticoagulant.

- The lupus anticoagulant (also known as lupus antibody) is an IgM or IgG immunoglobulin which binds to phospholipids and proteins associated with the cell membrane. Lupus anticoagulant is a misnomer as it is actually a prothrombotic agent. It produces a prolonged PTT by binding to the phospholipid used in the in vitro PTT assay; hence it is called lupus anticoagulant.

Etiology

- Lupus anticoagulant (LA) is seen in 20–45% of patients with systemic lupus erythematosus (SLE). Patients with HIV infection also have a high incidence of LA. Drugs such as procainamide, hydralazine, isoniazid, dilantin, phenothiazines, quinidine, and ACE inhibitors are known to induce LA.

Effects of Lupus Anticoagulant

- Some patients can be asymptomatic. Many elderly patients have lupus anticoagulant.
- LA is associated with antiphospholipid syndrome (APS or APLA). See APS for detailed clinical features.

Diagnosis

- Lupus anticoagulant should be suspected in cases of a markedly prolonged APTT without clinical bleeding. APTT fails to correct when the patient's plasma is mixed with normal plasma.
- The Russell viper venom (RVV) time is test of choice to detect the presence of lupus anticoagulant.
- Lupus anticoagulant can cause a false-positive VDRL test for syphilis.

Treatment

- Anticoagulant therapy should be started for patients with thrombosis. Heparin therapy is difficult to monitor due to already prolonged APTT and hence, low-molecular-weight heparin is preferred.

Q. Causes of splenomegaly.

Q. Differential diagnosis of massive splenomegaly.

Causes of Splenomegaly

Mild splenomegaly

- *Acute infections*: Typhoid, malaria, septicemia and subacute bacterial endocarditis

Moderate splenomegaly

- Leukaemia and lymphomas
- Polycythemia vera
- Hemolytic anemias
- Cirrhosis of liver
- Hemochromatosis
- Tumors and cysts
- Tuberculosis

Massive splenomegaly

- Chronic myeloid leukemia (CML)
- Myelofibrosis
- Gaucher's disease
- Chronic lymphocytic leukemia (CLL)
- Hairy cell leukemia
- Kala-azar (visceral leishmaniasis)
- Tropical splenomegaly syndrome (hyperreactive malarial splenomegaly syndrome)
- Thalassemia major
- AIDS with disseminated *Mycobacterium avium* complex infection.

Differential Diagnosis of Massive Splenomegaly

Chronic Myeloid Leukemia (CML)

Clinical features

- Median age at presentation is around 50 years.
- Patients may have systemic symptoms such as fatigue (due to anemia), malaise, weight loss, excessive sweating).
- Abdominal fullness and left hypochondral pain due to massive splenomegaly.
- Bleeding episodes due to platelet dysfunction.
- Moderate to massive splenomegaly with hepatomegaly
- Pallor due to anemia

Laboratory findings

- Normocytic normochromic anemia
- WBC count is markedly raised (usually >100,000).
- Platelet count may be raised, but in advanced disease falls.
- Peripheral smear shows presence of myelocytes and metamyelocytes.
- Philadelphia chromosome is positive in >95% cases.
- Leucocyte alkaline phosphatase (LAP) score is very low.

Myelofibrosis

Clinical features

- The median age at presentation is 67 years.
- The most common presenting complaint is severe fatigue.
- Hepatomegaly.

Laboratory findings

- Anemia
- WBC count is variable and thrombocytopenia is often present.
- Leucocyte alkaline phosphatase (LAP) score is increased.
- Peripheral smear shows teardrop-shaped RBCs, nucleated RBCs and granulocyte precursors (myelocytes, metamyelocytes, and blasts).
- Bone marrow is often difficult to aspirate, usually yielding a "dry" tap. Bone marrow biopsy shows extensive replacement of the marrow by fibrosis, which is the hallmark of the disease.

Gaucher's Disease

Clinical features

- It is an autosomal recessive disorder.
- Hepatosplenomegaly, anemia, thrombocytopenia, and bone disease.
- Bone manifestations include fractures, infarctions, and vertebral collapse.

Laboratory findings

- Thrombocytopenia and anemia.
- Liver enzymes may be mildly elevated.
- Acid phosphatase is elevated in patients with active bone disease.
- Reduced glucocerebrosidase activity in leukocytes.

Chronic Lymphocytic Leukemia (CLL)

Clinical features

- Painless lymphadenopathy.
- Weight loss, fever and night sweats without evidence of infection.
- Easy fatigability.
- Hepatomegaly may be present.

Laboratory findings

- Anemia.
- Increased WBC count.
- Thrombocytopenia.

Hairy Cell Leukemia

Clinical features

- The median age of presentation is approximately 55 years, with a male predominance.
- Symptoms include abdominal fullness, fatigue, weakness, weight loss, and bleeding tendency.
- Lymphadenopathy is unusual.

Laboratory features

- Pancytopenia.
- Peripheral smear shows malignant cells with cytoplasmic projections ("hairy cells").
- Bone marrow shows presence of hypercellularity and hairy cells.

Kala-azar (Visceral Leishmaniasis)

Clinical features

- Visceral leishmaniasis is a parasitic disease caused by the obligate intracellular protozoa *Leishmania*.
- It is also known as kala-azar (Hindi for black sickness or fever) and is a systemic disease that can be life-threatening.
- 90% of cases occur in Bangladesh, Northeastern India, Nepal, Sudan, and Northeastern Brazil.
- Clinical features are organomegaly, fever and cachexia.

Laboratory features

- Pancytopenia due to massive splenomegaly and bone marrow involvement.
- Hypergammaglobulinemia
- Abnormal liver function tests, hypoalbuminemia and hyperbilirubinemia.
- Antibodies against leishmania positive.
- A skin or bone marrow aspirate usually shows amastigotes.

Tropical Splenomegaly Syndrome (Hyperreactive Malarial Splenomegaly Syndrome)

Clinical features

- Patient is from malaria endemic area.
- Recurrent attacks of malaria in the past.

Laboratory features

- Pancytopenia.
- Peripheral smear may demonstrate malarial parasite.

Thalassemia Major

Clinical features

- Thalassemia is common in the Mediterranean region especially amongst Italians and Greeks. The thalassemia belt extends to India and Southeast Asia.
- Symptoms start late in the first year of life when fetal hemoglobin levels decline.
- Pallor, irritability, growth retardation, hepatosplenomegaly and jaundice develop due to severe hemolytic anemia.
- Characteristic chipmunk facies (frontal bossing and prominent check bones) due to bone marrow expansion.
- Eighty percent of untreated children die within the first five years of life, as a result of severe anemia, high output heart failure, and infections.

Laboratory features

- Signs of hemolysis such as anemia, increased indirect (unconjugated) bilirubin, increased LDH and reduced haptoglobin levels.
- Hemoglobin electrophoresis shows markedly reduced HbA and raised HbF.
- Peripheral smear shows hypochromia, microcytosis, anisopoikilocytosis, tear drop cells and target cells. WBC and platelet counts are normal unless hypersplenism develops.
- Bone marrow shows marked hypercellularity.
- The osmotic fragility test is significantly reduced.
- Skull X-ray shows widened diploic space and hair-on-end appearance. Compression fractures of the vertebrae and marked osteoporosis are common.

AIDS with Mycobacterium avium Complex

Clinical features
- Intermittent or persistent fever, fatigue, malaise, anorexia, and weight loss.
- Lymphadenopathy and hepatomegaly may be present.

Laboratory features
- HIV serology is positive.
- Anemia and neutropenia from bone marrow involvement.
- Elevated liver enzymes due to liver involvement.
- Blood culture is positive for nontuberculous mycobacteria.

Q. Hypersplenism.

- Spleen is the major organ of the monocyte/macrophage system.
- As the blood passes through the white and red pulp, old and defective blood cells are removed by the spleen. The macrophages in the spleen hold, retard, modify ("pitting"), or remove ("culling") old and senescent RBCs. The normal pitting function of the spleen removes nuclear residua (Howell-Jolly bodies) and the normal culling function of the spleen removes senescent RBCs.
- All these normal activities of the spleen can be markedly accentuated in a large spleen leading to pancytopenia (anemia, neutropenia and thrombocytopenia). This is called hypersplenism.
- *Treatment of hypersplenism*—the management of hypersplenism depends on the cause of splenomegaly and the severity of cytopenias. The anemia or pancytopenia is usually not very profound. However, splenectomy may be considered if the anemia or other cytopenia is very severe.

Q. Enumerate the causes of generalized lymphadenopathy.

Q. Differential diagnosis of generalized lymphadenopathy in an adult.

- Lymphadenopathy is classified as localized when it involves only one region and generalized when it involves more than one region.

Causes of Generalized Lymphadenopathy

- *Infections*: Disseminated tuberculosis, cat scratch disease, secondary syphilis, HIV, infectious mononucleosis, histoplasmosis, coccidioidomycosis, cryptococcosis, toxoplasmosis and leshmaniasis.
- *Malignancy*: Metastatic ca, lymphoma and leukemia.
- *Connective tissue diseases*: Rheumatoid arthritis, SLE and sarcoidosis
- *Endocrine disorders*: Hypothyroidism and Addison's disease
- *Drugs*: Allopurinol, hydralazine and phenytoin

Differential Diagnosis of Important Causes

HIV Infection

Clinical features
- Common in persons with high risk sexual behavior and intravenous drug addicts.
- Fever, weight loss, and chronic diarrhea may be present.
- Nontender lymphadenopathy primarily involving the axillary, cervical, and occipital nodes.

Lab features
- HIV-ELISA test positive.
- Western blot test confirms the diagnosis.

Disseminated Tuberculosis

Clinical features
- Nodes are typically nontender, enlarge over weeks to months without prominent systemic symptoms, and can progress to matting and fluctuation.
- Fever, weight loss and night sweats.
- Hepatosplenomegaly.

Lab features
- Montoux test may be positive.
- Chest X-ray may show military mottling.
- Lymph node or liver biopsy may show caseating granulomas.

Infectious Mononucleosis

Clinical features
- Triad of fever, pharyngitis, and lymphadenopathy.
- Maculopapular rash may be present.
- Lymphadenopathy is typically symmetric and involves the posterior cervical nodes more than the anterior group.
- Lymphadenopathy may also be present in the axillary and inguinal areas, which distinguishes infectious mononucleosis from other causes of pharyngitis.

Lab features
- Atypical lymphocytosis in the peripheral blood.
- Paul-Bunnell test and monospot test may be positive.

Systemic Lupus Erythematosus

- Nodes are soft, nontender, and discrete.
- Cervical, axillary, and inguinal areas are usually involved.
- Lymphadenopathy is more frequently noted at the onset of disease or in association with an exacerbation.
- Other features such as joint pain and rash (especially malar rash) may be present
- ANA and anti-ds DNA may be positive.

Brucellosis

Clinical features
- Fever, polyarthritis, hepatosplenomegaly
- Common in veterinary staff and slaughter house personnel.

Lab features
- Positive blood culture.
- Positive brucella agglutination test.

Lymphomas (Hodgkin and Non-Hodgkin)

Clinical features
- Constitutional symptoms like fever and weight loss.
- Painless rubbery lymphadenopathy, usually in the neck or supraclavicular fossae.
- Dry cough, breathlessness and dysphagia may occur due to medastinal lymphadenopathy.
- Hepatosplenomegaly may be present.

Lab features
- Normochromic, normocytic anemia.
- LDH may be raised.
- Lymph node biopsy confirms the disease. Characteristic Reed-Sternberg cells are found in Hodgkin lymphoma.

Chronic Lymphocytic Leukemia (CLL)

Clinical features
- More common in elderly males
- Recurrent infections are common due to immunodeficiency.
- Hepatosplenomegaly.

Lab features
- WBC count is usually greater than 20,000/μl.
- The hallmark of CLL is isolated lymphocytosis. Usually more than 75% of the circulating cells are lymphocytes.
- Bone marrow shows infiltration with lymphocytes.
- Lymph node biopsy shows well differentiated, small, non-cleaved lymphocytes.

CML in Blast Crisis

Clinical features
- Fever, hemorrhage, generalized lymphadenopathy, bone pain and sternal tenderness.
- Abrupt increase in spleen size.

Lab features
- Peripheral smear and bone marrow show more than 20% blasts.
- Philadelphia chromosome is positive in most cases.

Drugs

- Many drugs can cause serum sickness characterized by fever, arthralgias, rash, and generalized lymphadenopathy. Phenytoin can cause generalized lymphadenopathy in the absence of a serum sickness reaction.
- There is temporal correlation between drug intake and the onset of lymphadenopathy. Withdrawal of offending drug leads to resolution of lymphadenopathy.

Q. Indications and complications of blood transfusion.

Red Blood Cell Transfusions

- Red blood cell transfusions are given to raise the hematocrit levels in patients with severe anemia or to replace losses during acute bleeding episodes.
- Preparations containing red blood cells are mainly of three types.

Whole Blood

- Whole blood contains all components of blood such as red blood cells, plasma, and platelets. Whole blood transfusion is used during surgery and acute blood loss.

Packed Red Blood Cells

- Packed red cells do not contain any other component of blood. Each unit has a volume of about 300 ml, of which approximately 200 ml consists of red blood cells. Packed RBC transfusion is useful in patients with severe anemia who already have normal plasma volume.

Autologous Packed Red Blood Cells

- Patients scheduled for elective surgery may donate their own blood beforehand for transfusion during surgery. These units may be stored for up to 35 days.

Compatibility Testing

- Before transfusion, the recipient's and the donor's blood are cross-matched to avoid hemolytic transfusion reactions. Although many antigen systems are present on red blood cells, only the ABO and Rh systems are specifically tested prior to all transfusions.
- Incompatible blood transfusion can lead to severe blood transfusion reactions.

Complications of Blood Transfusion

- Transfusion reactions (hemolytic and non-hemolytic)
- Transmission of infections (hepatitis B, HIV, hepatitis C, malaria, syphilis, Creutzfeldt-Jakob disease and Chagas disease)

(contd.)

- Circulatory overload
- Hypocalcemia (due to citrate binding to calcium in stored blood)
- Hyperkalemia (due to potassium coming out of RBCs in stored blood)
- Hypothermia (due to massive blood transfusion of fridge stored blood)
- Thrombocytopenia (seen in massive blood transfusion because platelets do not survive for long in stored blood)
- Iron overload (seen in thalassemia due to recurrent blood transfusion)

Q. Hemolytic transfusion reactions.

- Severe hemolytic reactions occur if ABO incompatible blood is transfused. Most of these cases are due to clinical or laboratory errors or mislabeled specimens.
- Hemolysis is rapid and intravascular, releasing free hemoglobin into the plasma. Hemolytic transfusion reactions caused by minor antigen systems (such as Duffy, Kidd, Kell,) are less severe and hemolysis is extravascular.

Clinical Features

- Major hemolytic transfusion reactions cause fever and chills, flank pain and red or brown urine (due to hemoglobinuria).
- In severe cases, there may be apprehension, dyspnea, hypotension, vascular collapse, DIC, and acute renal failure. In patients under anesthesia or in coma, above signs may not be manifest and DIC may be the presenting mode, with oozing of blood from puncture sites and hemoglobinuria.

Laboratory Findings

- Evidence of renal failure and DIC.
- Plasma appears pink due to hemoglobinuria.
- Urine may show hemoglobinuria.
- Indirect bilirubin may be elevated due to hemolysis.

Treatment

- If a hemolytic transfusion reaction is suspected, blood transfusion must be immediately stopped.
- Identification of the recipient and of the blood should be checked. The donor transfusion bag and infusion set should be returned to the blood bank, along with a fresh blood sample of the patient for retyping and repeat cross-matching.
- Patient should be hydrated well to prevent renal failure due to hemoglobinuria. Forced alkaline diuresis may help prevent renal damage.

Q. Non-hemolytic transfusion reactions.

Leukoagglutinin Reactions

- These reactions occur due to antibodies formed in the recipient against antigens present on white blood cells of donor by previous transfusions.
- Patients will develop fever and chills and in severe cases, cough and dyspnea may occur. Chest X-ray may show transient pulmonary infiltrates. Since there is no hemolysis, Hb rises as expected after transfusion.
- Treatment involves antihistamines such as diphenhydramine, antipyretics (paracetamol) and corticosteroids. Removal of leukocytes by filtration before blood storage will reduce the incidence of these reactions.

Anaphylactic Reactions

- These reactions are usually due to plasma proteins present in the donor blood. Patients will develop urticaria or bronchospasm during a transfusion.
- These reactions respond to antihistamines and corticosteroids. There is no need to stop transfusion unless it is very severe. Patients with such reactions may require transfusion of washed red blood cells to avoid future severe reactions.

Reactions due to Contaminated Blood

- Transfusion of blood contaminated with bacteria (gram-negative) can lead to septicemia and shock from endotoxin.
- If this is suspected, the offending unit should be cultured and the patient treated with appropriate antibiotics.

Q. Transfusion-related acute lung injury (TRALI).

- Transfusion-related acute lung injury (TRALI) is a syndrome characterized by acute respiratory distress following transfusion. It is caused by anti-HLA and/or antigranulocyte antibodies in donor plasma that agglutinate and degranulate recipient granulocytes within the lung.

Clinical Features

- Incidence is 1 in 5,000 to one in 10,000, but many cases are mild. Mild to moderate transfusion-related acute lung injury probably is commonly missed.
- Symptoms of TRALI typically develop within 6 hours of a transfusion. Patients develop breathlessness. There may be associated fever, cyanosis, and hypotension. Examination reveals bilateral crepitations. Chest X-ray shows evidence of bilateral pulmonary edema (non-cardiogenic pulmonary edema or ARDS).

Treatment

- Treatment of TRALI is supportive. Mild forms of TRALI respond to oxygen supplementation. Severe forms may require mechanical ventilation and ICU support. Majority of patients recover within 72 to 96 hours.

Q. Transfusion of blood components.

Packed RBCs

- See above

Fresh Frozen Plasma

- Fresh frozen plasma (FFP) is prepared from single units of whole blood or from plasma collected by apheresis techniques. It is frozen at minus 18 to minus 30°C within eight hours of collection and, can be stored up to one year.
- FFP contains all of the coagulation factors present in the blood.
- ABO compatibility is required before transfusion, but Rh typing is not required.
- A dose of 10 to 15 ml/kg (3–5 units) will correct coagulation abnormality.

Indications

- Bleeding due to excess warfarin, vitamin K deficiency, or deficiency of multiple coagulation factors (e.g. DIC, liver disease, dilutional coagulopathy)
- Treatment of TTP-HUS
- Factor XIII deficiency
- Factor VIII deficiency
- Factor IX deficiency

Platelet Concentrate (PC) or Platelet Rich Plasma (PRP)

- One unit is made from four or five donations of whole blood, or from a single platelet apheresis technique.
- Stored at 20–24°C and must be kept agitated to avoid clumping.
- Shelf life up to 5 days from collection.
- ABO compatibility is required, though ABO incompatible platelets can be used.
- One unit of platelet concentrate generally increases platelet count by 4000–8000/mm^3.

Indications

- Bleeding due to thrombocytopenia or platelet dysfunction. Platelets should be transfused irrespective of bleeding when count is <10,000/mm^3.
- Prior to surgery in thrombocytopenic patients.

Cryoprecipitate

- Prepared by precipitating plasma at near freezing point.
- Contains fibrinogen, factor VIII, factor IX and von Willebrand's factor.

Indications

- Fibrinogen deficiency.
- von Willebrand's disease and haemophilia A and B if recombinant products are not available.

7 Diseases of Liver and Biliary System

Q. Enumerate the functions of liver.

Metabolism
- Carbohydrate
- Protein
- Lipids
- Drugs and alcohol
- Hormones

Excretion
- Bile salts
- Bilirubin

Synthesis
- Albumin
- Coagulation factors
- Complement factors
- Haptoglobin
- Ceruloplasmin
- Transferrin
- Bile acids

Storage
- Iron
- Copper
- Vitamins A, D and B_{12}

[Remember the pnemonic **MESS**, **M** = metabolism, **E** = excretion, **S** = synthesis, **S** = storage]

Q. What are the signs and symptoms of liver disease?

Symptoms
- Jaundice (acute hepatitis, decompensated cirrhosis, liver abscess, liver metastases, obstructive jaundice).
- Easy fatigability and malaise.
- Altered mental status (due to hepatic encephalopathy).
- Pruritus (in obstructive jaundice).
- Abdominal distension (ascites, hepatomegaly).
- Light-colored stools (in obstructive jaundice).
- Bleeding tendency (due to reduced synthesis of clotting factors).

Signs
- Peripheral edema (cirrhosis with portal HTN).
- Gynecomastia (chronic liver disease).
- Spider angioma (acute or chronic liver disease).
- Palmar erythema (chronic liver disease).
- Flapping tremors (hepatic encephalopathy).
- Ascites (cirrhosis of liver with portal HTN).
- Right upper quadrant tenderness (acute hepatitis, fatty liver, congested liver, hepatic abscess).
- Hepatomegaly (fatty liver, acute hepatitis, hepatoma, liver metastases, liver abscess, congestive hepatomegaly in CCF).

Q. Liver function tests (LFTs).

Q. Diagnostic tests for the evaluation of liver disease.

Liver function tests are done for following purposes:
- Detecting hepatic dysfunction.
- Assessing the severity of liver injury.
- Monitoring the course of liver diseases and the response to treatment.
- Refining the diagnosis.

Tests for Liver Injury

Aminotransferases (Transaminases): AST and ALT
- Normal circulating liver enzyme levels are due to enzymes released during normal hepatocyte turnover. These liver enzymes are increased during liver cell injury or death.
- Normal serum levels are 5–40 IU/L (international units per liter).
- Serum AST and ALT level increases in acute hepatocyte injury due to viruses (viral hepatitis), toxins (alcohol, drugs) and ischemia (ischemic hepatitis). Elevated ALT is somewhat specific for liver injury. Because AST is present in the heart, skeletal muscle, kidneys, and pancreas, elevated AST may reflect rhabdomyolysis or injury to one of these organs.

- Enzymes are usually less than 200 to 300 IU/L in alcoholic hepatitis where as they are 1000 IU/L or more in acute viral hepatitis or shortly after acute biliary obstruction, for example, during passage of a gallstone. Aminotransferase levels may be low in massive hepatic necrosis because liver injury is so extensive that a little enzyme activity remains.
- Aminotransferase levels can be used to monitor activity of chronic liver disease such as chronic hepatitis B or C.
- In most liver diseases, the ratio of AST to ALT is usually less than or equal to 1. However, ratios are usually 2 or more in alcoholic fatty liver and alcoholic hepatitis, reflecting increased synthesis as well as secretion of mitochondrial AST into plasma and selective loss of ALT activity due to pyridoxine deficiency seen in alcoholism. An elevated AST/ALT ratio can also be found in fulminant hepatitis due to Wilson's disease.

Tests for Cholestasis

Alkaline Phosphatase

- Alkaline phosphatases can be found in many organs (liver, bile ducts, intestine, bone, kidney, placenta, and leukocytes). Serum alkaline phosphatase mainly comes from liver and bone.
- It catalyzes the release of phosphate from ester substrates at an alkaline pH.
- The normal level in adults is less than 110 IU/L. Alkaline phosphatase levels are elevated in cholestatic hepatobiliary diseases. Modest increases (up to 3 times normal) occur in many hepatic parenchymal disorders, such as hepatitis and cirrhosis. Larger increases (3 to 10 times normal) are seen in biliary obstruction. Major elevations also occur with intrahepatic cholestasis and with infiltrative or mass lesions (malignancy, lymphoma, leukemia). It is also elevated in bone disorders (Paget's disease, osteomalacia, bone metastases), during rapid bone growth in children, pregnancy, and chronic renal failure.
- To know whether elevated ALP is due to hepatobiliary disease, levels of 52-nucleotidase can be measured. If 52-nucleotidase levels are also elevated along with ALP, it means ALP elevation is due to hepatobiliary disease.

5′-nucleotidase

- 5′-nucleotidase is a plasma membrane enzyme which cleaves phosphate from the 52 position from adenosine or inosine phosphate. Its levels are elevated in cholestasis. Its major use is to confirm whether an elevated serum alkaline phosphatase is hepatic in origin. It can be increased in late pregnancy.

Gamma-glutamyl Transpeptidase (GGT)

- The normal range is 0 to 51 international units per liter (IU/L).
- GGT is present in many tissues. Its level is increased in hepatobiliary diseases, but is not specific to hepatobiliary diseases. It can also be elevated in myocardial infarction, neuromuscular diseases, pancreatic disease, pulmonary disease, and diabetes. Its levels are especially elevated in alcoholic liver disease. Hence, it is sometimes used for monitoring abstinence from alcohol. GGT levels parallel those of ALP; hence, it can be used to confirm whether ALP elevation is due to hepatobiliary disease.

Tests to Assess Metabolic Function

- Bilirubin, ammonia and various drugs are metabolized or detoxified in the liver. Serum levels of these metabolites can be a sensitive indicator of liver disease.

Bilirubin

- Normally, total bilirubin is mostly unconjugated, with values of <1.2 mg/dl.
- Direct hyperbilirubinemia is seen in cholestatic hepatobiliary diseases and Dubin-Johnson disease.
- Indirect hyperbilirubinemia is found in Gilbert's syndrome, Crigler-Najjar syndrome, and hemolysis.
- High bilirubin levels correlate with a poorer prognosis in alcoholic hepatitis, primary biliary cirrhosis, and fulminant hepatic failure.

Ammonia

- Ammonia is a byproduct of amino acid metabolism and is removed from blood by the liver, converted to urea in Krebs cycle, and excreted by the kidneys. Normal serum level is 15–45 micrograms per deciliter (μg/dl).
- Ammonia levels are elevated in liver dysfunction and portosystemic shunting. Measurements of blood ammonia are used to confirm a diagnosis of hepatic encephalopathy and to monitor the success of therapy.
- Elevated ammonia levels also occur when ammonia production is increased by intestinal flora (e.g. after a high-protein meal or gastrointestinal bleeding), by the kidney (in response to metabolic alkalosis or hypokalemia), or in rare genetic diseases that affect urea cycle.

Drug Clearance

- Bromosulfophthalein (BSP) clearance can quantify hepatic function, but rarely used in clinical practice.

Tests for Hepatic Synthetic Function

Prothrombin Time

- Prothrombin time (PT) reflects the plasma concentrations of factors VII, X, and V, prothrombin, and fibrinogen.

- Normal value is 11–13.5 seconds, or INR (international normalized ratio) of 0.8–1.1.
- Since clotting factors are synthesized in liver, a prolonged PT occurs in liver diseases. Prolonged PT can also occur due to vitamin K deficiency, one cause of which is malabsorption from cholestatic liver disease since bile juice is important for the absorption of this fat soluble vitamin.

Serum Albumin Level

- The normal range is 3.5–5.5 grams per deciliter (g/dl). Albumin is produced solely by the liver. Hence, albumin levels can be decreased in liver dysfunction and there will be reversal of albumin globulin ratio (normal 2:1).
- Other causes of low albumin are nephrotic syndrome, protein-losing enteropathy, severe burns, exfoliative dermatitis, and major gastrointestinal bleeding.

Liver Biopsy

- Liver biopsy is useful in the diagnosis of diffuse or localized parenchymal diseases, including chronic hepatitis, cirrhosis, and malignancy.
- Liver biopsy for diffuse disease can be done blindly. However, localized disease such as tumors requires biopsy under ultrasound or radiographic guidance. Liver biopsy can also be done under direct visualization during laparoscopy or laparotomy.
- Contraindications include coagulopathy, high-grade biliary obstruction, and biliary sepsis.

Other Tests Used in Liver Disease (not Included Under Liver Function Tests)

Examinations of Urine and Stool

- Bilirubinuria indicates increase in plasma conjugated bilirubin levels. Stool occult blood may be positive due to portal gastropathy, portal hypertension and GI malignancy which might have metastasized to liver. Malena indicates upper GI bleed.

Hematologic Tests in Liver Disease

- Anemia can occur due to bleeding esophageal varices, hypersplenism or bone marrow suppression by alcohol. Pancytopenia can occur due to hypersplenism or bone marrow suppression by alcohol.
- Target cells (erythrocytes with an expanded cell membrane) may be found in chronic liver disease due to abnormalities in serum lipids. Spur cells (acanthocytes) can occur in advanced alcoholic cirrhosis.

Tests for Specific Liver Diseases

- Specific tests for viral antigens, nucleic acids, and antibodies are available for the hepatitis viruses (hepatitis A, B, C, D, E) as well as Epstein-Barr virus, cytomegalovirus and herpesviruses.
- Antimitochondrial antibodies are virtually diagnostic of primary biliary cirrhosis. Antinuclear, anti-smooth muscle, and anti-liver microsomal antibodies are present in autoimmune hepatitis.
- Iron studies may help to rule out hemochromatosis. Serum copper and ceruloplasmin levels may help to rule out Wilson's disease.

Q. Describe the liver function tests in acute hepatitis and obstructive jaundice.

LFTs in Acute Hepatitis

- The serum aminotransferases AST and ALT (previously called SGOT and SGPT) are increased in acute hepatitis (400 to 4000 IU or more). Patients with viral hepatitis usually have aminotransferases greater than 500 U/L, with the ALT greater than or equal to the AST. Patients with alcoholic hepatitis usually have an AST at least 2 times more than ALT.
- Serum alkaline phosphatase is normal or only mildly elevated.
- Bilirubin level in acute hepatitis range from 5 to 20 mg/dl. Jaundice is usually visible in the sclera or skin when the serum bilirubin is more than 2.5 mg/dl. Both conjugated and unconjugated bilirubin rise in acute hepatitis.
- Prothrombin time (PT) may be prolonged and reflects a severe hepatic synthetic defect, signifies extensive hepatocellular necrosis, and indicates a worse prognosis.
- Serum albumin is usually normal in acute viral hepatitis. Globulin levels may be mildly elevated.

LFTs in Obstructive Jaundice

- AST and ALT are only moderately elevated in biliary obstruction.
- Serum alkaline phosphatase is markedly elevated (>3–10 times normal). 5′-nucleotidase and gamma-glutamyl transferase are also elevated and usually parallel that of alkaline phosphatase.
- Conjugated bilirubin is more than unconjugated bilirubin.
- Prothrombin time (PT) may be prolonged secondary to vitamin K malabsorption because bile juice is required for the absorption of this fat soluble vitamin.
- Serum albumin and globulin levels are usually normal.

7

Q. Endoscopic retrograde cholangiopancreatography (ERCP).

- ERCP is a procedure where a specialized side-viewing endoscope is passed into the second part of duodenum allowing for instruments to be passed into the bile or pancreatic ducts. A small catheter can be introduced into the bile or pancreatic duct, and radiographic contrast medium is injected under fluoroscopic monitoring to visualize the pancreatic and biliary tree. A very fine caliber "baby" endoscope can also be introduced into the duct of interest for direct visualization.
- ERCP is a technically demanding procedure, and there is risk of serious complications (e.g. pancreatitis).

Indications for ERCP

- Endoscopic therapy of postoperative biliary leaks and strictures.
- Identifying and treating underlying cause in patients with recurrent acute pancreatitis.
- Treatment of symptomatic strictures in chronic pancreatitis.
- Diagnosis and treatment of symptomatic pancreatic duct stones.
- Treatment of pancreatic duct disruptions or leaks by placement of bridging or transpapillary pancreatic stents.
- Draining symptomatic pancreatic pseudocysts.
- Removal of stones from CBD.
- Palliation of biliary obstruction in patients with pancreatic or biliary cancer.
- Tissue sampling in patients with pancreatic, biliary and ampullary cancers.
- Biliary pancreatitis.
- Patients with type I sphincter of Oddi dysfunction (SOD) respond to ERCP-guided sphincterotomy.

Complications for ERCP

- Pancreatitis
- Bleeding
- Sepsis
- Perforation

Q. Magnetic resonance cholangiopancreatography (MRCP).

- MRCP is a new noninvasive technique for evaluating the intrahepatic and extrahepatic bile ducts and the pancreatic duct.
- MRCP is a digital reconstruction technique based on an abdominal MRI scan. It is noninvasive and has excellent sensitivity and specificity. Unlike ERCP, MRCP does not require contrast material to be administered into the ductal system. However, MRCP does not allow any intervention to be performed, such as stone extraction, stent insertion, or biopsy.
- Because of its relative safety, it is useful for screening patients with a low likelihood of disease. In those with a higher probability, ERCP is still the procedure of choice because of its therapeutic options.
- MRCP has lower resolution than conventional direct cholangiography and can miss small stones (<4 mm), small ampullary lesions, primary sclerosing cholangitis, and strictures of the ducts. MRCP also has difficulty visualizing small stones in the pancreatic duct.

Q. Percutaneous transhepatic cholangiography (PTC).

- PTC is an invasive technique requiring transhepatic insertion of a needle into a dilated bile duct under ultrasound or MRI guidance, followed by injection of contrast material to opacify the bile ducts. It is done under local anesthesia.
- PTC is useful in patients who have biliary duct dilation on ultrasonography or other imaging test but not candidates for ERCP.
- PTC is more accurate than ultrasonography or CT scan for identifying the cause and site of biliary tract obstruction. However, PTC is technically more difficult and has more complications.
- PTC can also be used for therapeutic interventions like drainage of infected bile in cholangitis, extraction of biliary tract stones, dilation of benign biliary strictures, or placement of a stent across a malignant stricture.
- Complications include bacteremia, and hemobilia.

Q. Endoscopic ultrasound (EUS).

- Endoscopic ultrasound (EUS) is a technique where an ultrasound transducer is attached to the tip of an endoscope and passes into the upper gastrointestinal (GI) tract to obtain echo images. EUS examination resembles standard endoscopy of the upper gastrointestinal tract.
- It provides good resolution images of the gut wall and the surrounding organs and blood vessels.
- It is useful to evaluate pancreas, bile ducts, for obtaining FNAC, etc.

Q. Indications and contraindications of liver biopsy.

Liver biopsy can be done by many methods: Percutaneous, transjugular, laparoscopic, or ultrasound or CT-guided fine needle aspiration (FNA). Percutaneous liver biopsy is the simplest and most commonly performed approach.

Indications for Liver Biopsy

- Diagnosis, grading and staging of liver diseases, such as chronic hepatitis B or C, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), hemochromatosis or Wilson's disease.
- Unexplained liver disease or abnormal liver function tests.
- Monitoring the liver following a liver transplant.
- Diagnosis of a liver mass.
- Pyrexia of unknown origin.

Contraindications for Liver Biopsy

- Significant blood clotting abnormalities.
- Severe anemia.
- Severe obstructive jaundice.
- Severe ascites.
- Severe kidney failure.
- Excessive obesity.
- Local skin infection at the biopsy site.
- Suspected hemangioma or vascular tumor.
- Uncooperative patient.

Q. Discuss the metabolism of bilirubin.

- Bilirubin is the degradation product of the heme moiety of hemoproteins. Normal adults produce about 4 mg bilirubin per kg body weight per day. 70 to 90% of bilirubin comes from degradation of hemoglobin and the remainder comes from the degradation of nonhemoglobin hemoproteins such as myoglobin, the P-450 cytochromes, catalase, and peroxidase.
- Heme is converted to biliverdin (green pigment) by *heme oxygenase*. Biliverdin is nontoxic and water-soluble. Biliverdin is converted to bilirubin by *biliverdin reductase*. Bilirubin is bound to albumin in plasma and transported to liver.
- The total plasma bilirubin concentration in normal adults is less than 1.5 mg/dl. Most of the plasma bilirubin is unconjugated and only a small fraction is conjugated. Unconjugated bilirubin is also called indirect bilirubin because it reacts very slowly with diazo reagent used to estimate the amount of bilirubin in plasma. Conjugated bilirubin is also called direct bilirubin because it reacts fast with diazo reagent without the addition of agents such as ethanol or urea. The "indirect"-reacting bilirubin is calculated by subtracting the direct-reacting bilirubin from the total.
- In the liver, uptake of unconjugated bilirubin from plasma happens by a facilitated transport process and to a lesser extent by diffusion. Liver converts unconjugated bilirubin into conjugated bilirubin mono- and diglucuronides by a specific UDP-glucuronyl transferase. These bilirubin mono- and diglucuronides are transported into bile by a canalicular membrane ATP-dependent transporter. Conjugation of bilirubin makes it more soluble and enhances its elimination from the body. Conjugated bilirubin is loosely bound to albumin and can be excreted by the kidneys. Hence, bilirubinuria is found in obstructive or cholestatic jaundice. Newborn infants have decreased capacity to conjugate bilirubin which leads to unconjugated hyperbilirubinemia (physiologic jaundice of the newborn). If severe, this can lead to CNS damage (kernicterus). Exposure to blue light (phototherapy) converts bilirubin to water-soluble photoisomers which are easily excreted in bile, thereby decreasing CNS damage.
- Following canalicular secretion, conjugated bilirubin enters the biliary tree, reaches the duodenum, and passes down the gastrointestinal tract without reabsorption by either the gallbladder or intestinal mucosa. In the gut (ileum and colon), most of the conjugated bilirubin is converted into urobilinogen by bacteria. Urobilinogen is reabsorbed by the intstine, returns to the liver through

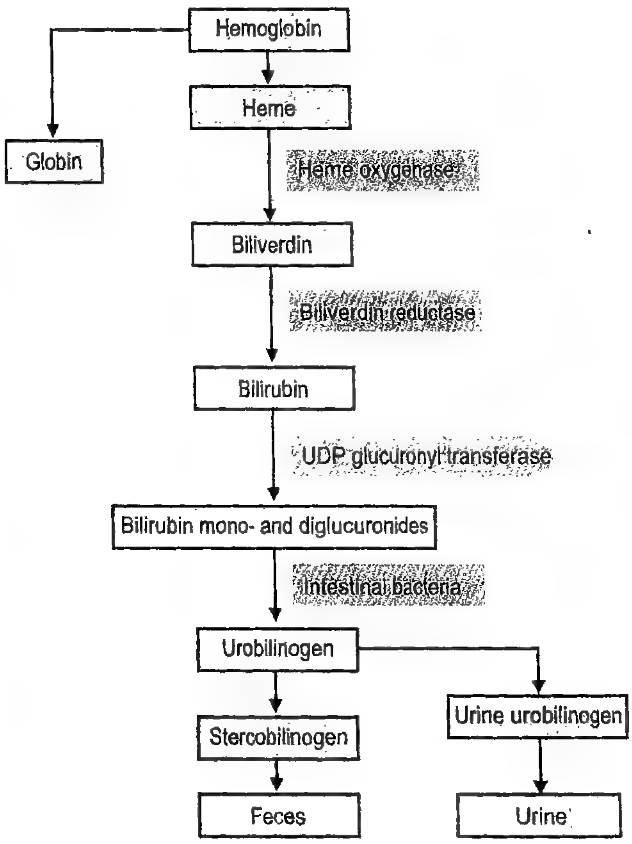

Fig. 7.1: Bilirubin metabolism

the portal circulation, and is re-excreted into bile (enterohepatic recirculation). Any urobilinogen not taken up by the liver is cleared by the kidneys.

- Urine urobilinogen is increased in hemolysis, which increases the load of bilirubin entering the gut and therefore the amount of urobilinogen formed and reabsorbed, and in liver disease due to reduced extraction of urobilinogen by the liver leading to increased excretion by the kidneys. In obstructive jaundice, conjugated bilirubin does not enter the gut; hence there is no formation of urobilinogen leading to reduced excretion of urobilinogen in the urine.
- Gilbert's syndrome and Crigler-Najjar syndrome types 1 and 2 are characterized by unconjugated hyperbilirubinemia due to genetic defects in bilirubin conjugation. In contrast, Dubin-Johnson syndrome is characterized by conjugated or mixed hyperbilirubinemia due to defects in excretion of conjugated bilirubin into the bile.

Q. Van den Bergh reaction.

- Van den Bergh reaction is a method used to estimate bilirubin concentration in the plasma. This test involves the reaction of bilirubin with a diazo compound (diazotized sulfanilic acid), producing azopigments which can be quantified by spectrophotometry. Conjugated bilirubin reacts directly with diazo compound without the addition of alcohol hence it is also called direct bilirubin. Unconjugated bilirubin requires the addition of alcohol and hence called indirect bilirubin.
- The indirect and direct bilirubin can be distinguished based upon their rate of production in the presence or absence of alcohol. The fraction produced within one minute without the addition of alcohol represents the concentration of direct bilirubin. Fast reaction of direct bilirubin is due to the absence of internal hydrogen bonding and water solubility. Total bilirubin is that amount that reacts in 30 minutes after the addition of alcohol. Indirect bilirubin is calculated by subtracting direct bilirubin from total bilirubin. Total bilirubin concentration by this technique is usually below 1 mg/dl.
- Van den Bergh reaction slightly overestimates direct bilirubin because a fraction of unconjugated bilirubin also gives a direct reaction. Endogenous substances, such as plasma lipids, and drugs, such as propranolol, can interfere with the diazo reaction and produce unreliable results. Bilirubin complexed to albumin (delta bilirubin) also may give a direct reaction.

Q. Enumerate the causes of tender hepatomegaly.

Viral hepatitis
Acute alcoholic hepatitis
Hepatic amoebiasis
Liver abscess
Acute fatty liver
Congestive cardiac failure
Hepatocellular carcinoma
Actinomycosis of the liver
Weil's disease (leptospirosis)

Q. Enumerate the causes of jaundice. How do you approach a case of jaundice?

- Jaundice is defined as yellowish discoloration of skin, mucous membranes and sclera due to hyperbilirubinemia. Hyperbilirubinemia may be due to abnormalities in the formation, transport, metabolism, and excretion of bilirubin. Total serum bilirubin is normally 0.3–1 mg/dl. Jaundice is clinically detectable when levels are more than 2.5 mg/dl.

Causes of Jaundice

Predominantly unconjugated hyperbilirubinemia

- *Increased production*: Hemolysis, breakdown of hematomas, ineffective erythropoiesis.
- *Impaired hepatic uptake*: Congestive heart failure, portosystemic shunts, drugs such as rifampin, probenecid, flavaspadic acid.
- *Impaired conjugation*: Crigler-Najjar syndrome type I and II, Gilbert's syndrome, neonates, hyperthyroidism, estrogens, acquired transferase deficiency—chronic hepatitis, cirrhosis.

Predominantly conjugated hyperbilirubinemia

- *Intrahepatic causes*: Dubin-Johnson syndrome, Rotor's syndrome, progressive familial intrahepatic cholestasis syndromes and benign recurrent intrahepatic cholestasis, cirrhosis, drugs, sepsis, postoperative jaundice, and sarcoidosis.
- *Extrahepatic causes*: Choledocholithiasis, biliary atresia, carcinoma of biliary duct, sclerosing cholangitis, choledochal cyst, external pressure on common duct, pancreatitis, Ca head of pancreas, periampulary carcinoma.

Approach to a Case of Jaundice

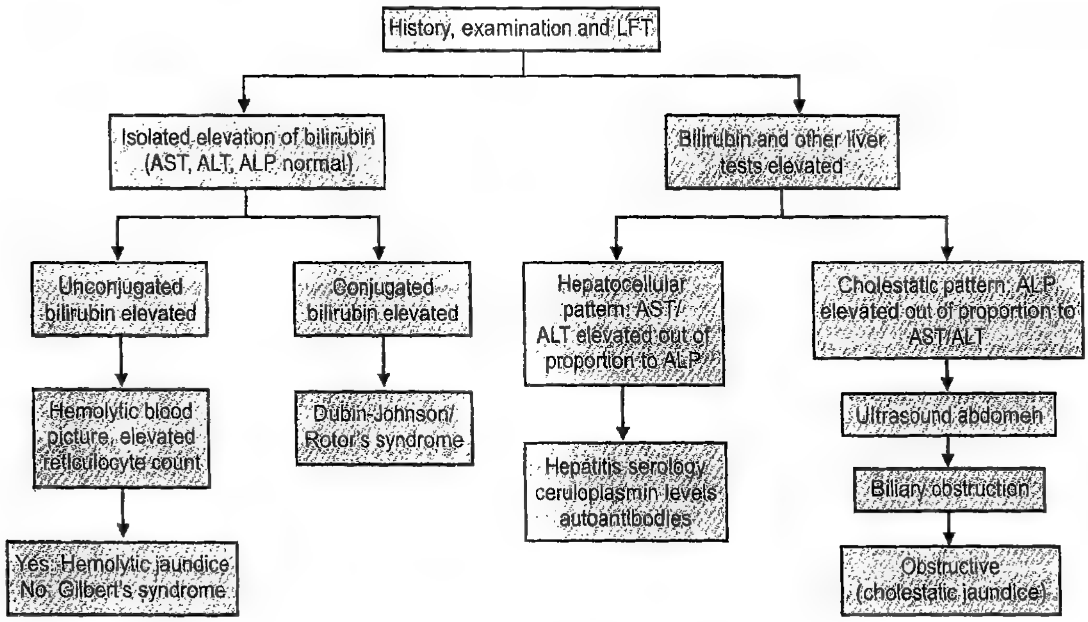

Fig. 7.2: Approach to a case of jaundice

Q. Discuss briefly the congenital hyperbilirubinemic disorders.

Table 7.1 Congenital hyperbilirubinemic disorders

	Inheritance	Defect	Type of hyperbilirubinemia	Features
Gilbert's syndrome	Autosomal dominant	Mild deficiency of UDP-glucuronyl transferase	Unconjugated	Benign, asymptomatic jaundice. More common in males. Urobilinogen in the urine is increased but there is no bilirubinuria. Peripheral blood smear, reticulocyte count and haptoglobin are normal (suggesting absence of hemolysis). Hyperbilirubinemia increases after fasting. No treatment required (phenobarbital can increase the activity of UDP-glucuronyl transferase). Prognosis excellent.
Crigler-Najjar syndrome type I	Autosomal recessive	Complete absence of UDP-glucuronyl transferase	Unconjugated	Seen in infants. Bilirubin is very high (20 to 25 mg/dl, can be as high as 50 mg/dl). Stool color is normal, but fecal urobilinogen excretion is diminished due to the marked reduction in the conjugation of bilirubin. Peripheral blood smear, reticulocyte count and haptoglobin are normal (suggesting absence of hemolysis). Prognosis poor. Death occurs due to kernicterus, unless vigorously treated.
Crigler-Najjar syndrome type II	Autosomal recessive	Partial absence of UDP-glucuronyl transferase	Unconjugated	Usually benign, kernicterus occurs rarely. Hyperbilirubinemia can be reduced by treatment with phenobarbital.

(contd.)

Table 7.1 Congenital hyperbilirubinemic disorders (*contd.*)

	Inheritance	Defect	Type of hyperbilirubinemia	Features
Dubin-Johnson syndrome	Autosomal recessive	Reduced ability to transport conjugated bilirubin into biliary canaliculi	Conjugated	Benign, asymptomatic jaundice. Gallbladder not visualized on oral cholecystography. BSP (bromsulphalein) test shows reduced clearance. Liver darkly pigmented on gross examination. Biopsy shows centrilobular brown pigment. No treatment required. Prognosis excellent
Rotor's syndrome	Autosomal recessive	Faulty excretory function of hepatocytes	Conjugated	Similar to Dubin-Johnson syndrome, but liver is not pigmented and the gallbladder is visualized on oral cholecystography. Prognosis excellent

Q. Discuss the clinical and laboratory differentiation of different types of jaundice.

Table 7.2 Clinical and laboratory differentiation of different types of jaundice

Clinical features	Hemolytic	Hepatocellular	Obstructive
• Color of jaundice	Lemon yellow	Orange yellow	Greenish yellow
• Depth of jaundice	Mild	Moderate	Deep
• Pruritus	Absent	Sometimes	Present
• Bleeding tendency	Absent	Present	Present (late)
• Bradycardia	Absent	Absent	Present
• Pallor	Present	Absent	Absent
• Splenomegaly	Present	Sometimes	Absent
• Features of liver cell failure	Absent	Present	Present (late)
• Stool color	Normal	Normal	Light color (clay color)
• Urine color	Normal	Dark	Dark
Laboratory features			
• Bilirubin	Predominantly unconjugated	Mixed	Predominantly conjugated
• ALT, AST	Normal	Markedly increased	Minimally increased
• Alkaline phosphatase	Normal	Increased	Markedly increased
• Serum albumin	Unchanged	Decreased	Unchanged
• Prothrombin time	Normal	Prolonged and does not respond to parenteral vitamin K	Prolonged in late stages and responds to parenteral vitamin K
• Urine bilirubin	None	Increased	Increased
• Urine urobilinogen	Increased	Increased	Absent

Q. Describe the etiology, epidemiology, clinical features, laboratory features and treatment of hepatitis A. Add a note on its prevention.

Many viruses can cause viral hepatitis. These are as follows:

- *Hepatitis viruses*: Hepatitis A, B, C, D, E.
- *Other viruses*: Cytomegalovirus, Epstein-Barr virus, herpes simplex virus, yellow fever virus.

Hepatitis A

Etiology

- Hepatitis A is caused by the hepatitis A virus which is a RNA virus that belongs to the family of Picornaviridae.
- It is resistant to freezing, detergents and acids. It can be inactivated by heat (>85°C, formalin and chlorine.
- Replication occurs in the liver. The virus is secreted into the bile and found in stool. Highest titers are found in stool during the incubation period and early symptomatic phase of illness.

Epidemiology

- It is transmitted almost exclusively by the fecal-oral route and rarely through blood transfusion. Most is due to direct person-to-person exposure, and to lesser extent, to direct fecal contamination of food or water. Consumption of shellfish from contaminated waterways is also a rare source of hepatitis A infection.
- People at risk of acquiring hepatitis A include travelers to developing countries, children in day care centers, men who have sex with men, injection drug users, hemophiliacs given plasma products, and persons in institutions.
- It is more prevalent in low socioeconomic groups in which a lack of adequate sanitation and poor hygienic practices facilitate spread of the infection.

Clinical Features

- Incubation period is 15 to 45 days (mean 30 days).
- HAV infection usually results in an acute, self-limited illness and only rarely leads to fulminant hepatic failure. Fulminant hepatic failure is likely to occur when hepatitis A infection is superimposed on pre-existing chronic hepatitis B or hepatitis C.
- Symptomatic infection is more common in adults than children. Jaundice occurs in 70% of adults infected with HAV but in smaller proportions of children.
- Illness begins with the abrupt onset of prodromal symptoms including, fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain. Dark urine, jaundice, and pruritus develop in a few days. Prodromal symptoms decrease as the jaundice appears.
- Physical examination shows jaundice and hepatomegaly. There may be splenomegaly, and cervical lymphadenopathy.
- Hepatitis A does not lead to chronic infection, chronic hepatitis, cirrhosis or carrier state.
- There can be extrahepatic manifestations such as vasculitis, arthritis, optic neuritis, transverse myelitis, thrombocytopenia, aplastic anemia, and red cell aplasia.

Laboratory Findings

- Serum aminotransferases are markedly elevated (peak levels vary from 400 to 4,000 IU). ALT (SGPT) is more elevated than AST (SGOT). Aminotransferase elevations precede the bilirubin elevation. Bilirubin is elevated (up to 30 mg/dl) and is usually equally divided between the conjugated and unconjugated fractions. ALP is normal or mildly elevated. Other laboratory abnormalities are increased CRP, ESR and immunoglobulins.
- Prothrombin time (PT) may be prolonged and signifies extensive hepatocellular necrosis and worse prognosis
- IgM anti-HAV antibody appears early in the disease and persists for 4 to 12 months. It can be used for the diagnosis of acute hepatitis A. IgG antibodies also appear early in the course and persists for life. Other viral markers such as HbsAg, anti-HCV and anti-HEV should be done to rule out other causes of viral hepatitis.
- Imaging studies such as ultrasound abdomen are done if there is possibility of an alternative diagnosis. It may show hepatomegaly in acute hepatitis.

Treatment

- The disease is usually self-limited, and treatment is mainly supportive with hydration, vitamins and antipyretics.
- Liver transplantation should be considered for patients who develop fulminant liver failure.

Prevention of Hepatitis A

- Improvement of sanitation, handwashing before eating, heating foods appropriately, and avoidance of water and foods from endemic areas prevent the transmission of virus. Chlorination and household bleach (1:100 dilution) inactivate the virus.
- *Vaccine*: A safe and effective HAV vaccine is available (HAVRIX by GlaxoSmithKline). It is given as two injections 6 months apart (1.0 ml intramuscular). It is recommended for patients at high risk of acquiring hepatitis A such as travelers to endemic areas, children in communities with high rates of infection, men who have sex with men, injection drug users, patients with chronic liver disease and recipients of pooled plasma products, such as hemophiliacs.

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- *Post-exposure prophylaxis*: Vaccine is not effective for post-exposure prophylaxis because antibodies take a few days to develop. Immune globulin is recommended for post-exposure prophylaxis of household and intimate contacts of persons with acute hepatitis A. The dose is 2 ml given intramuscularly within 2 weeks of exposure. Concurrent HAV vaccination is also appropriate.

Q. Describe the etiology, epidemiology, pathogenesis, clinical features, laboratory features and treatment of hepatitis B.

Q. Prevention of hepatitis B.

Hepatitis B is an acute systemic infection which primarily affects liver.

Etiology

Hepatitis B is caused by the hepatitis B virus (HBV) which is a DNA virus belonging to the family of Hepadnavirus. It has double-stranded DNA, inner core-protein (hepatitis B core antigen, HBcAg), and outer surface coat (hepatitis B surface antigen, HBsAg).

Epidemiology

- Incubation period is about 90 days (50–150 days).
- The virus infects only humans and higher apes.
- It is transmitted by percutaneous, perinatal, and sexual routes.
- Persons at risk of developing infection include; spouse of an acutely infected person, unprotected sex with multiple partners (especially men who have sex with men), health care workers, injection drug users, recipients of repeated transfusions, especially with pooled blood concentrates (e.g. hemophiliacs), dentists, prisoners, family members of chronically infected persons, persons on hemodialysis, being born to an infected mother.
- Prevalence is high in sub-Saharan Africa and Southeast Asia, Down syndrome, lepromatous leprosy, leukemia, Hodgkin's disease, polyarteritis nodosa, patients receiving hemodialysis, injection drug users, lower socioeconomic groups, and older age groups.

Pathogenesis

The pathogenesis of HBV-related liver disease is largely due to immune-mediated mechanisms resulting in destruction of HBV-infected hepatocytes by cytotoxic T cells. Rarely HBV can cause direct cytotoxic liver injury.

Clinical Features

- Clinical features are similar to hepatitis A.
- About 70% of patients with acute hepatitis B have subclinical or anicteric hepatitis, while 30% develop icteric hepatitis. The disease is more severe in patients with underlying liver disease.

Laboratory Findings

- Liver function tests are same as described in hepatitis A.
- Presence of HBsAg confirms the diagnosis of hepatitis B infection. Presence of IgM anti-HBc indicates acute infection. Presence of serum IgG anti-HBc indicates chronic hepatitis B infection. Presence of HBeAg is associated with high infectivity. Serum anti-HBsAg indicates immunity and found during recovery from hepatitis B and after vaccination.
- HBV-DNA by PCR is helpful when hepatitis B is strongly suspected inspite of negative HBsAg. It is also useful to monitor the disease activity and response to treatment.

Treatment

Same as acute hepatitis A.

Complications

- Serum sickness—like syndrome.
- Glomerulonephritis with nephrotic syndrome.
- Polyarteritis nodosa—like systemic vasculitis.
- Fulminant hepatitis (massive hepatic necrosis).
- Chronic hepatitis B (persistence of HBeAg beyond 3 months or HBsAg beyond 6 months).
- Atypical pneumonia.
- Aplastic anemia.
- Transverse myelitis.

Prognosis

- 95–99% of patients recover completely.
- Fulminant hepatitis: 0.1–1%
- Chronic hepatitis: 1–10%
- Carrier state: 0.1–30%

Prevention

Pre-exposure Prophylaxis

- Recombinant hepatitis B vaccine (e.g. Engerix B), 1 ml (20 μg) given IM at 0, 1, and 6 months.
- Alternative schedules have been approved, including accelerated schedules of 0, 1, 2, and 12 months and of 0, 7, and 21 days plus 12 months. Vaccine should be given to deltoid and not gluteal region. A booster dose is required after 5 years. Half the dose is given for children.
- Vaccination is indicated for high risk groups. But nowadays hepatitis B vaccination is being given to all.

Post-exposure Prophylaxis

- Hepatitis B immunoglobulin: 0.06 ml/kg IM should be given within 1 week after exposure, followed by a complete course of hepatitis B vaccine started within the first week. After sexual exposure immunoglobulin can be given up to 14 days.
- For perinatal exposure of infants born to an HBsAg-positive mother, a single 0.5 ml IM dose of immunoglobulin should be given immediately after birth in combination with a complete course of 3 injections of hepatitis B vaccine to be started within the first 12 hours of life.

Q. Australia antigen; HBsAg; hepatitis B surface antigen.

- Hepatitis B surface antigen (HBsAg) is located in the capsular material of the virus.
- It is the serologic hallmark of HBV infection. It can be detected by radioimmunoassay (RIA) or enzyme immunoassay (EIA).
- HBsAg appears in serum 1 to 10 weeks after an acute exposure to HBV, before the onset of symptoms.
- In patients who recover, HBsAg usually becomes negative after three to six months. Persistence of HBsAg for more than six months indicates chronic hepatitis B. Usually less than 1% of patients progress to chronic hepatitis B.
- The disappearance of HBsAg is followed by the appearance of anti-HBs indicates recovery from hepatitis B infection.
- Since antibodies against HBsAg are protective against hepatitis B, HBsAg is used in the manufacturing of hepatitis B vaccines.

Q. Chronic hepatitis B carrier.

Q. Conditions associated with hepatitis B carrier state.

- After hepatitis B infection, HBsAg disappears from the blood in 3–6 months in 90% of adults. But in 10% the virus persists for more than 6 months; these persons are called chronic carriers.
- The prevalence of chronic carrier state is low in low endemicity countries (1% in America, Europe, Australia), 1–6% in intermediate-endemicity countries (India, Middle East, Russia), and 7–30% in high-endemicity countries (Africa, China, Taiwan).
- The carrier state usually lasts indefinitely but HBsAg occasionally disappears spontaneously (1% per year). About 10–20% of chronic carriers are HBeAg-positive and highly infectious.
- Liver biopsy in the majority (80%) of chronic carriers is nearly normal (asymptomatic carriers) but in about 20% changes of chronic hepatitis are present.
- LFT (ALT) should be monitored in carriers every 6–12 months.

Conditions associated with hepatitis B carrier state (risk factors for chronic carrier status)

- Male gender.
- Anicteric acute hepatitis B.
- After perinatal transmission.
- Patients treated with steroids.
- Impaired cell-mediated immunity (e.g. chronic uremia, malignancy, lepromatous leprosy, Down's syndrome).

Q. Describe the etiology, epidemiology, clinical features, laboratory features and treatment of hepatitis C.

Hepatitis C is an acute systemic infection caused by the hepatitis C virus (HCV) which primarily affects the liver. It was previously called non-A, non-B hepatitis.

Epidemiology

- Prevalence is about 170 million cases worldwide.
- Frequency is higher among African Americans and Mexican Americans than white persons.
- Most frequent in persons 30–50 years of age.
- More frequent in men than women.
- Transmitted by percutaneous, perinatal, and sexual routes (just like hepatitis B).
- Persons at risk of acquiring infection are same as those in hepatitis B.
- Breastfeeding does not increase risk.

Etiology

Hepatitis C is caused by HCV which is a RNA virus belonging to Flaviviridae family.

Clinical Features

- Incubation period is 15–150 days (mean, 50 days).
- Other clinical features are similar to hepatitis A.

Investigations

- LFTs are similar to other viral hepatitis.
- Diagnosis of hepatitis C can be made by demonstrating the presence of serum anti-HCV. Diagnosis is confirmed with HCV RNA testing which is the gold standard for establishing the diagnosis of hepatitis C.
- Hepatitis A and hepatitis B should be ruled out by appropriate tests (*see* above).

- In patients with significant cholestasis, ultrasound abdomen and imaging of the biliary tree may be indicated to rule out obstruction from stone or neoplasm.
- Liver biopsy is rarely necessary.

Treatment

- Supportive care.
- Antiviral therapy: Treatment of acute hepatitis C patients with peginterferon or interferon alpha for 6–24 weeks decreases the risk of chronic hepatitis. Because 20% of patients with acute hepatitis C clear the virus spontaneously, it is better to wait for 3–4 months before starting interferon. Ribavirin may be added if HCV RNA fails to clear after 3 months of peginterferon or interferon alpha.
- Liver transplantation is indicated for patients with fulminant hepatic failure and severe encephalopathy.

Complications

- Essential mixed cryoglobulinemia.
- Immune complex disease (arthritis, cutaneous vasculitis, glomerulonephritis).
- B cell lymphoma.
- Fulminant hepatitis (massive hepatic necrosis).
- Chronic hepatitis C (50–70%).
- Pancreatitis.
- Myocarditis.
- Atypical pneumonia.
- Aplastic anemia.
- Transverse myelitis.
- Peripheral neuropathy.

Prevention

- No active or passive immunization available for hepatitis C.
- Universal precautions should be adhered to while handling patients.
- Other general preventive measures include safe sexual practices, using disposable needles, etc.

Q. Delta hepatitis (hepatitis D).

Delta hepatitis is an acute systemic infection caused by hepatitis D virus (HDV) which primarily affects the liver.

Etiology

- Delta hepatitis is caused by HDV which is a defective RNA virus belonging to the genus Deltavirus and an unclassified family.
- HDV requires the helper function of HBV (or other hepadnaviruses) for its replication and expression. It can infect a person simultaneously with HBV (co-infection) or superinfect a person already infected with HBV (superinfection).
- Because HDV relies absolutely on HBV, the duration of HDV infection is determined by the duration of HBV infection.
- HDV increases the severity of HBV infection and accelerates the progression of chronic hepatitis to cirrhosis.

Epidemiology

- About 10 million people are infected worldwide. Incidence is decreasing now.
- HDV infection is endemic among persons with hepatitis B. 5–8% of hepatitis B chronic carriers have anti-HDV.
- It is endemic in Mediterranean countries (Northern Africa, Southern Europe, the Middle East).
- HDV infection is common in persons exposed frequently to blood and blood products (injection drug users and hemophiliac persons).

Risk Factors

- Persons infected with hepatitis B.
- Close personal contact with people with HDV.
- Frequent exposure to blood or blood products.

Clinical Features

- *Incubation period*: 30–180 days.
- Other clinical features are similar to hepatitis A.

Investigations

- Presence of HDV infection can be identified by anti-HDV seroconversion (an increase in titer of anti-HDV or *de novo* appearance of anti-HDV). It may take 30–40 days for anti-HDV to appear in acute infection.
- Tests for the presence of HDV-RNA are useful for determining the presence of ongoing HDV replication and relative infectivity.
- Demonstration of intrahepatic HDV antigen in liver biopsy.
- Other tests are similar to other viral hepatitis.

Treatment

Same as acute hepatitis A.

Prevention

- In HBV-negative persons, hepatitis B vaccine can prevent hepatitis D infection.
- In HBV-positive persons, there is no product to prevent HDV superinfection. Avoidance of percutaneous exposures and limitation of intimate contact with persons who have HDV infection are recommended.

Q. Hepatitis E.

Hepatitis E is an acute systemic infection caused by the hepatitis E virus (HEV) which primarily affects the liver.

Etiology

- Hepatitis E virus is a nonenveloped single-stranded RNA virus.
- It was previously classified under Caliciviridae family, but now classified under the group, "Hepatitis E-like viruses".
- Transmitted by fecal-oral route by eating or drinking contaminated food or water.
- HEV is excreted in the stool during the late incubation period.

Epidemiology

- Highest incidence of HEV infection is in Asia, Africa, Middle East, and Central America.
- Most epidemics in developing countries are due to contaminated drinking water (e.g. after monsoon flooding).
- Several reports suggest a zoonotic reservoir for HEV in swine.

Clinical Features

- Highest attack rate is between 15 and 40 years of age.
- *Incubation period*: 15–60 days.
- Fulminant hepatic failure occurs more frequently during pregnancy with hepatitis E, resulting in high mortality rate especially in the third trimester. Reasons for this are unknown.
- Other clinical features are similar to viral hepatitis A.

Investigations

Diagnosis is established by detection of the HEV genome in serum or feces by PCR or by the detection of IgM antibodies to HEV.

Treatment

Same as acute hepatitis A.

Prevention

- Vaccine is under development.
- Travelers to endemic areas should avoid drinking water of unknown purity, uncooked shellfish, and uncooked fruits or vegetables.

Q. Define chronic hepatitis.

Q. Discuss the causes, pathology, clinical features, investigations and management of chronic hepatitis.

Definition

Chronic hepatitis is hepatitis that lasts >6 months.

Etiology

- Viruses (hepatitis B, C, D).
- Drugs (isoniazid, nitrofurantoin, amiodarone, methotrexate).
- Alcoholic steatohepatitis.
- Nonalcoholic steatohepatitis (NASH).
- Metabolic causes (Wilson's disease, hemochromatosis, α_1-antitrypsin deficiency, primary biliary cirrhosis, sclerosing cholangitis).
- Autoimmune hepatitis.
- Cryptogenic hepatitis.

Clinical Features

- Many patients are asymptomatic.
- Some may have malaise, anorexia, fatigue, low-grade fever and nonspecific upper abdominal discomfort.
- Jaundice is usually absent. Signs of chronic liver disease (e.g. splenomegaly, spider nevi, palmar erythema) or complications of cirrhosis (e.g. portal hypertension, ascites, encephalopathy) may be present in advanced cases.

Investigations

- Liver function tests show elevation of liver enzymes such as AST and ALT.
- Viral serologic tests.
- Autoantibodies, immunoglobulins, α_1-antitrypsin level, and other tests.
- Liver biopsy.

Treatment

- Supportive care.
- Treatment of cause (e.g. corticosteroids for autoimmune hepatitis, antivirals for HBV and HCV infection, withdrawal of offending drug in drug induced chronic hepatitis).
- Corticosteroids and immunosuppressants should be avoided in chronic hepatitis B and C because these drugs enhance viral replication.

Prognosis

Drug induced chronic hepatitis often regresses completely when the causative drug is withdrawn. Untreated chronic viral hepatitis can lead to cirrhosis or development of hepatocellular carcinoma.

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Q. Discuss the clinical features, investigations and management of chronic hepatitis B.

- Hepatitis B is considered chronic when HBsAg persists for more than 6 months.
- Liver injury and pathogenesis of chronic hepatitis B are immunologically mediated. Antigen-specific cytotoxic T cells mediate the cell injury in hepatitis B and also account for ultimate viral clearance. The progression of acute to chronic hepatitis B is attributed to lack of a vigorous cytotoxic T cell response to hepatitis B antigens.

Epidemiology

- Chronic hepatitis B afflicts 400 million people worldwide. Persons at high risk of chronic hepatitis B include men who have sex with men, persons with multiple sexual partners, hemophiliacs, oncology and renal dialysis patients, and health care workers.
- Most patients with chronic hepatitis B eventually recover. But some may progress to cirrhosis and end-stage liver disease. Some patients may go into an inactive carrier state with no symptoms, normal serum aminotransferase levels, and inactive liver disease on liver biopsy.

Clinical Features

- Many patients with chronic hepatitis B are asymptomatic.
- Symptomatic patients may present with constitutional symptoms such as fatigue, malaise, low grade fever, anorexia and jaundice which is persistent or intermittent.
- Stigmata of chronic liver disease such as hepatomegaly, palmar erythema, and spider angioma may be present.
- Some patients may present with features of cirrhosis with portal HTN.
- The extrahepatic manifestations of chronic hepatitis B include mucocutaneous vasculitis, glomerulonephritis, and polyarteritis nodosa.

Investigations

- HBsAg, HBeAg, and HBV-DNA persist, generally at high levels. There are two general forms of chronic hepatitis B. HBeAg-positive chronic hepatitis B, in which there are high levels of HBV-DNA, and less commonly HBeAg-negative form, where there are moderate levels of HBV-DNA in serum.
- Aminotransferases (ALT, AST) remain elevated. But one-third of patients may have normal or near-normal aminotransferases.
- Alkaline phosphatase level is normal or marginally elevated.
- Serum bilirubin level is normal to moderately elevated.
- Hypoalbuminemia is present.
- Prothrombin time is prolonged.
- Ultrasound abdomen or CT scan are useful to rule out hepatocellular carcinoma and to guide liver biopsy.
- Liver biopsy may be indicated to assess severity of disease, predict response to therapy, or rule out hepatocellular carcinoma.

Treatment of Chronic Hepatitis B

Indications for treatment as recommended by WHO include the following:

- All patients with chronic hepatitis B and cirrhosis should be treated, regardless of ALT levels, HBeAg status or HBV-DNA levels.
- Treatment is recommended for patients with chronic hepatitis B without cirrhosis, but are aged more than 30 years, with persistently abnormal ALT levels, and evidence of high-level HBV replication (HBV-DNA >20,000 IU/ml), regardless of HBeAg status.
- Currently, pegylated interferon alpha (PEG-IFN-α), entecavir, and tenofovir are the first-line agents in the treatment of hepatitis B disease.

Entecavir

- It is considered a first-line treatment for HBV infection.
- Entecavir is a nucleoside analogue and inhibits HBV-DNA polymerase. It has a high antiviral potency, and resistance to it is uncommon.
- Adverse effects include exacerbations of hepatitis B virus infection after discontinuation, lactic acidosis and severe hepatomegaly with steatosis.

Tenofovir

- Tenofovir has replaced adefovir (an older nucleotide analogue) as a first-line treatment. It is a nucleotide analogue (adenosine monophosphate) reverse transcriptase and hepatitis B virus (HBV) polymerase inhibitor. Tenofovir is the most potent oral antiviral for hepatitis B; resistance to it is minimal.
- It has a few adverse effects. Its main side effects are lactic acidosis and severe hepatomegaly with steatosis. The dose is 300 mg once daily orally.

Telbivudine

It is a newer nucleoside analog that has greater efficacy and potency than lamivudine but also has a high rate of resistance; it is not considered first-line treatment. Dosage is 600 mg orally once/day.

Alpha-interferon

- This is effective in patients with a low viral load and elevated serum transaminases. However, it is not the first-

choice treatment. It acts by augmenting the native immune response. Interferon therapy is not recommended in patients with normal or near-normal serum aminotransferase levels (even if HBeAg is present) because it is usually ineffective in this situation. Interferon has to be given by subcutaneous injection.

- It is given for 4–6 months in HBeAg-positive chronic hepatitis in whom the response is good. Response rates are lower in HBeAg-negative chronic hepatitis, even with longer duration of therapy.
- Longer-acting pegylated interferons which can be given once weekly have been developed and are effective in both HBeAg-positive and HBeAg-negative chronic hepatitis.
- Interferon is contraindicated in the presence of decompensated cirrhosis (e.g. ascites, jaundice, coagulopathy, encephalopathy). In such patients, it can precipitate liver failure.

Lamivudine

- It is no longer considered first-line treatment for HBV infection because risk of resistance is higher and efficacy is lower than those of newer antiviral drugs.
- It is a nucleoside analogue which inhibits DNA polymerase and suppresses HBV-DNA levels. It can be given even in decompensated cirrhosis and improves liver function. It may prevent the need for liver transplantation.
- Long-term therapy is complicated by the development of HBV-DNA polymerase mutants.
- Lamivudine is recommended in a dose of 100 mg/day for 1 year.
- Entecavir and telbivudine are other nucleoside analogues effective against hepatitis B.

Adefovir

- Adefovir has been replaced by tenofovir. It is a nucleotide analogue which inhibits HBV-DNA polymerase. It reduces HBV-DNA levels, and leads to histological improvement.
- Adefovir is effective against lamivudine-induced DNA polymerase mutant viruses.
- It can be used in the presence of decompensated cirrhosis but is contraindicated in renal failure.
- Dosage is 10 mg daily for 1 year.

Combination Therapy

Studies of combination therapy are underway.

General Measures

- All household and sexual contacts of patient should be vaccinated.
- Vaccination against hepatitis A also is recommended.
- Patients with hepatitis B should avoid all but the most necessary use of immunosuppressive medications. Severe flares of hepatitis B and even deaths have followed short courses of corticosteroids or cancer chemotherapy.

Q. Chronic hepatitis C.

- Chronic hepatitis C is diagnosed when hepatic inflammation and necrosis continue for ≥6 months.
- Mild chronic hepatitis C is nonprogressive or only slowly progressive. Severe chronic hepatitis C can lead to cirrhosis, liver failure, or hepatocellular carcinoma.

Epidemiology

- Chronic hepatitis C develops in up to 85% of patients with acute hepatitis C. Worldwide 170 million people are infected. It may be the most common cause of chronic hepatitis. It is the most frequent indication for liver transplantation.
- Most frequent in persons 30–50 years of age.
- More frequent in men than women.

Clinical Features

Same as chronic hepatitis B.

Investigations

- Serologic markers of HCV (anti-HCV) infection remain positive even after 6 months. HCV-RNA also remains detectable.
- Aminotransferases (ALT, AST) remain elevated. But one-third of patients may have normal or near-normal aminotransferases.
- Alkaline phosphatase level is normal or marginally elevated.
- Serum bilirubin level is normal to moderately elevated.
- Hypoalbuminemia may be present.
- Prothrombin time may be prolonged.
- Autoantibodies such as rheumatoid factor can be present and needs to be differented from rheumatoid arthritis in patients with arthralgias.
- Ultrasound abdomen or CT scan is useful to rule out hepatocellular carcinoma and to guide liver biopsy.
- Liver biopsy may be indicated to assess severity of disease, predict response to therapy, or rule out hepatocellular carcinoma.

Treatment

- Because spontaneous resolution is common, waiting 2–4 months after the onset of illness is recommended.

- Indications for therapy include persistent elevation of ALT, portal/bridging fibrosis or moderate to severe hepatitis on liver biopsy and detectable HCV-RNA.
- Earlier treatment options included a combination of ribavirin and pegylated interferon. Recently, many protease inhibitors effective against hepatitis C virus have been introduced. Some of the combinations regimens recommended are as follows:
  - Combination of paritaprevir, dasabuvir and ribavirin daily for 3 to 6 months.
  - Combination of sofosbuvir plus simeprevir with or without ribavirin daily for 3 to 6 months.
  - Pegylated interferon (SC once weekly) plus ribavirin plus sofosbuvir daily.

Q. Chronic hepatitis D.

- Chronic hepatitis D is diagnosed when hepatic inflammation and necrosis continue for ≥6 months after infection.
- HDV co-infection may increase the severity of acute hepatitis B, but it does not increase the likelihood of progression to chronic hepatitis B.

Epidemiology

- Worldwide ~10 million people are affected.
- HDV infection is endemic among persons with hepatitis B.
- Because HDV relies absolutely on HBV, the duration of HDV infection is determined by the duration of HBV infection.

Clinical Features

Clinical and biochemical features are same as those of chronic hepatitis B.

Investigations

Anti-HDV and HDV-RNA are positive. In addition, markers of hepatitis B are also positive.

Treatment

- Interferon alpha or peginterferon alpha with or without adefovir is effective against hepatitis D, but patients may relapse and tolerance is poor.
- Lamivudine is not effective.
- Clevudine is undergoing trials and preliminary results indicate that it is effective.

Q. Drug and toxin-induced hepatotoxicity (hepatitis).

- Drug and toxin-induced hepatotoxicity is defined as any degree of liver injury caused by a drug or a toxic substance.
- Many therapeutic agents can cause hepatic injury. Drug-induced liver disease can mimic viral hepatitis, biliary tract obstruction, or other types of liver disease.
- Mechanism of hepatocellular injury may be divided into two broad groups:
  1. Direct hepatotoxicity
  2. Idiosyncratic reactions (immune-mediated hyper-sensitivity).
- *Direct hepatotoxicity*: Here the hepatotoxicity is predictable, dose dependent and can affect all individuals if a high dose is taken. Examples are acetaminophen (paracetamol) alcohol, carbon tetrachloride, chloroform, heavy metals, phosphorus, valproic acid, and vitamin A.
- *Idiosyncratic reactions (immune-mediated hypersensitivity)*: Here the hepatotoxicity is not predictable, sporadic, and not related to dose. Occasionally it is associated with features of allergic reaction, such as fever and eosinophilia. In some patients, liver damage is from a metabolite that is produced only in certain individuals on a genetic basis. Examples are amiodarone, disulfiram, halothane, isoniazid, pyrazinamide, and streptomycin.

Types of Hepatotoxicity

Hepatocellular (elevated ALT)

- Paracetamol
- Halothane
- Isoniazid
- Rifampicin
- Pyrazinamide
- Alcohol
- Estrogens
- Anabolic steroids
- Erythromycin
- Chlorpromazine

Cholestatic (elevated alkaline phosphatase and total bilirubin)

- Amoxicillin/clavulanate
- Anabolic steroids
- Chlorpromazine
- Clopidogrel
- Oral contraceptives
- Erythromycin
- Estrogens
- Phenothiazines

Mixed (elevated alkaline phosphatase and ALT)

- Amitriptyline
- Azathioprine
- Carbamazepine
- Phenytoin
- Sulfonamides

Treatment

- Main treatment is withdrawal of the offending drug.
- N-acetylcysteine is useful in paracetamol toxicity.
- Supportive therapy for the specific type of liver injury.

Q. Acute liver failure.

Q. Define fulminant hepatic failure. Discuss the causes, pathology, clinical features, investigations and management of fulminant hepatic failure.

Definition

- Acute liver failure is rapid deterioration of liver function resulting in coagulopathy and encephalopathy in a previously healthy individual. It includes fulminant and subfulminant hepatic failure.
- *Fulminant hepatic failure* refers to the development of acute liver failure with superimposed hepatic encephalopathy developing within 8 weeks after the onset of acute liver disease in a patient without pre-existing liver disease.
- *Subfulminant hepatic failure* (or *late-onset hepatic failure*) refers to liver failure developing more slowly after 8 weeks up to 3 to 6 months.

Etiology

Drugs and Toxins

Acetaminophen (paracetamol) overdose, phosphorus poisoning (rat poison), *Amanita phalloides* mushroom toxin.

Viruses

- Hepatitis A, B, D and E
- Epstein-Barr virus
- Cytomegalovirus
- Herpes simplex virus
- Varicella zoster

Vascular

- Portal vein thrombosis
- Budd-Chiari syndrome (hepatic vein thrombosis)
- Ischemic hepatitis

Metabolic

- Wilson's disease
- Acute fatty liver of pregnancy
- Reye's syndrome

Miscellaneous

Malignant infiltration of the liver, sepsis, and autoimmune hepatitis.

Remember the pnemonic

A—Acetaminophen, hepatitis A, autoimmune hepatitis
B—Hepatitis B, Budd-Chiari syndrome
C—Cryptogenic, hepatitis C, cytomegalovirus
D—Hepatitis D, drugs
E—Esoteric causes—Wilson's disease, Budd-Chiari syndrome
F—Fatty infiltration—fatty liver of pregnancy, Reye's syndrome

Clinical Features

- Jaundice is often present.
- Liver may be enlarged and tender especially in acute hepatitis. An enlarged liver may be also be seen with congestive heart failure and Budd-Chiari syndrome. Liver size may decrease when there is significant loss of volume due to hepatic necrosis.
- Ascites may be present.
- *Hepatic encephalopathy*: This may range from mild alteration of consciousness to deep coma. Recognition of hepatic encephalopathy is central to the diagnosis of fulminant hepatic failure. Hepatic encephalopathy is mainly due to development of cerebral edema.
- *Coagulopathy*: Since the synthesis of most of the clotting factors occurs in the liver, liver failure leads to development of coagulopathy. Prothrombin time is prolonged. Patient may have bleeding from any site but upper GI bleed is common presenting as hematemesis and melena.
- Renal failure is common due to development of hepatorenal syndrome.
- Systemic inflammatory response syndrome with DIC and multiple organ dysfunction is common. This may occur with or without an underlying infection. ARDS and respiratory failure contribute to high mortality in fulminant hepatic failure.
- Metabolic derangements such as hyponatremia and hypoglycemia are common. Hyponatremia is mainly due to water retention. Hypoglycemia is due to depleted hepatic glycogen store, impaired gluconeogenesis and hyperinsulinemia. Hypokalemia, hypophosphatemia and metabolic alkalosis may also be present.
- Hypotension and hyperdynamic circulation are usually present due to peripheral vasodilatation. Adrenal insufficiency is common in liver failure and may contribute to hypotension.

Investigations

Findings are same as in acute viral hepatitis.

Treatment

- Treatment of underlying cause is most important.
- Maintenance of proper fluid and electrolyte balance.

- Support of nutrition (through Ryle's tube), respiratory and hemodynamic function.
- *Management of encephalopathy*: Cerebral edema is the most common cause of death in acute liver failure. Intracranial pressure can be monitored by an epidural catheter. Cerebral edema can be decreased by hyperventilation and mannitol (0.5 to 1 mg/kg body weight 8th hourly). If there is no response to above measures, pentobarbital coma should be induced using a bolus of 3 to 5 mg/kg intravenously. Since there is evidence that ammonia plays major role in the development of hepatic encephalopathy, elevated ammonia levels should be reduced with enteral administration of lactulose. Bowel wash can reduce intestinal bacterial load and decrease the production of ammonia. Administration of antibiotics such as neomycin orally or metronidazole can sterilize the bowel and decrease ammonia production by bacteria. Sedatives should be avoided if possible.
- *Management of renal failure*: Hemodialysis should be considered for renal failure.
- *Management of coagulopathy*: If there is active bleeding clotting factors should be replaced by transfusion of fresh frozen plasma (FFP). Vitamin K should be given parenterally to help in the synthesis of clotting factors. Recombinant factor VIIa may be used intravenously in patients who do not respond to FFP.
- Liver transplantation is the definitive treatment in liver failure. It should be considered in all patients with fulminant hepatic failure.

Prognosis

Prognosis is poor and mortality can be as high as 80%.

Q. Reye syndrome.

- Reye syndrome is a rare form of acute encephalopathy and fatty infiltration of the liver that tends to occur after some acute viral infections, particularly when salicylates are used.
- The exact cause is unknown, but usually follows chickenpox or influenza infection. Use of salicylates (aspirin) during the above infections is a major precipitating factor for the development of Reye syndrome.
- Pathologically fatty degeneration of liver, astrocyte edema and loss of neurons in the brain, and edema and fatty degeneration of the kidneys is seen. Hepatic mitochondrial dysfunction results in hyperammonemia, which is thought to induce astrocyte edema, resulting in cerebral edema and increased intracranial pressure (ICP).
- It is usually seen in children <18 years. Acute encephalopathy with cerebral edema develops. Clinical features include nausea, vomiting, headache, excitability, delirium, and combativeness with frequent progression to coma.
- Incidence has now decreased as aspirin use in patients with varicella or influenza has decreased.
- The mortality rate in Reye's syndrome is approximately 50%.
- Treatment is mainly supportive and includes intravenous hydration, infusions fresh-frozen plasma, and intravenous mannitol to reduce cerebral edema.

Q. Discuss fatty liver (hepatic steatosis) and its causes.

Q. Alcoholic fatty liver or alcoholic steatosis.

Q. Nonalcoholic fatty liver disease (NAFLD).

- Abnormal accumulation of fat (triglycerides) in the liver is called fatty liver.
- It can be divided into two types based on the size of fat droplets in the hepatocytes: (1) Microvesicular (small fat droplets in hepatocytes) and (2) Macrovesicular (large fat droplets in hepatocytes).
- When fatty liver is not due to alcohol, it is known as nonalcoholic fatty liver disease (NAFLD). Nonalcoholic steatohepatitis (NASH) is a type of NAFLD where fatty liver is associated with necroinflammatory activity.
- Macrovesicular fatty liver is the most common type of fatty liver seen. Here liver microscopy shows hepatocytes with large, empty vacuoles with the nucleus "pushed" to the periphery of the cell.
- Fatty liver is a benign disease and carries good prognosis. However, if the underlying cause is not treated (e.g. alcohol) it may progress and result in significant fibrosis and even cirrhosis.

Causes of Fatty Liver (Hepatic Steatosis)

Microvesicular
- Reye's syndrome
- Acute fatty liver of pregnancy
- Jamaican vomiting sickness
- Drugs (valproate, tetracycline)
- Hepatotoxins (e.g. phosphorus, petrochemicals)

Macrovesicular
- Alcohol
- Diabetes mellitus
- Obesity
- Lipodystrophy
- Dysbetalipoproteinemias
- Protein-energy malnutrition
- Starvation
- Prolonged parenteral nutrition
- Jejunoileal bypass
- Rapid weight loss
- Inflammatory bowel disease
- Drugs (methotrexate, vitamin A, glucocorticoids)

Clinical Features

- The signs and symptoms of fatty liver depend on the severity and the underlying cause. Many patients are asymptomatic. Liver is enlarged, firm and usually nontender. However, mild tenderness may be present in some patients.
- Rapid accumulation of fat (e.g. hyperalimentation, hepatotoxins) may lead to marked liver tenderness, due to stretching of Glisson's capsule.
- The clinical presentation of fatty liver from hepatotoxins is similar to that of fulminant hepatic failure with jaundice, hepatic encephalopathy, prolonged prothrombin time and increased aminotransferases.

Investigations

- Liver function tests are usually normal or show mild elevations of alkaline phosphatase or aminotransferases.
- Fatty liver can be detected by CT, MRI, or ultrasound.
- If there is doubt about the diagnosis, liver biopsy will show increased fat content, presence of any fibrosis, and possibly the underlying primary disorder.

Treatment

- Underlying cause should be treated (e.g. removal of alcohol or offending toxins, control of diabetes, weight loss in obesity, etc.).
- Adequate nutrition should be provided.

Q. Nonalcoholic steatohepatitis (NASH).

- Nonalcoholic steatohepatitis (NASH) is a syndrome that develops in patients who are not alcoholic and is characterized by fat accumulation and inflammation in the liver.

Risk Factors

- Obesity, type 2 diabetes mellitus, dyslipidemia, and/or metabolic syndrome.

Pathophysiology

- There is steatosis due to triglyceride accumulation, inflammation, and fibrosis. Steatosis is due to reduced synthesis of very low density lipoprotein (VLDL) and increased hepatic triglyceride synthesis. Inflammation may result from lipid peroxidative damage to cell membranes. These changes can stimulate hepatic stellate cells, resulting in fibrosis. NASH can progress to cirrhosis and portal hypertension.

Clinical Features

- NASH most often occurs in patients between 40 years and 60 years of age but can occur in all age groups.
- Most patients are asymptomatic.
- Some have fatigue, malaise, or right upper quadrant abdominal discomfort. Hepatomegaly is present in most patients.
- Splenomegaly may be present due to development of cirrhosis and portal hypertension.

Investigations

- Liver function tests show elevation of AST and ALT. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) may also be high.
- Serologic tests to rule out hepatitis B and C.
- FBS, PPBS, HbA1C.
- Lipid profile.
- Ultrasound abdomen, CT, and particularly MRI, can identify fatty liver.
- Liver biopsy shows large fat droplets (macrovesicular fatty infiltration) and inflammation.

Treatment

- For NASH, there is no specific treatment. Elimination of causes and control of risk factors such as discontinuation of drugs or toxins, weight loss, and treatment for dyslipidemia or hyperglycemia is the main treatment.
- Thiazolidinediones and vitamin E can help correct biochemical and histologic abnormalities in NASH.
- Many other treatments such as ursodeoxycholic acid, metformin, and betaine are not effective.

Q. Discuss the etiology, pathology, clinical features, investigations, complications and management of cirrhosis of liver.

Q. Child-Turcotte-Pugh scoring system.

- Cirrhosis refers to a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules.
- It represents the final common pathway of many types of chronic liver injury.

Causes of Cirrhosis

Infectious diseases
- Hepatitis B, C, D
- Cytomegalovirus
- Epstein-Barr virus
- Schistosomiasis
- Brucellosis
- Echinococcosis
- Toxoplasmosis

(contd.)

Drugs and toxins
- Alcohol (Laennec's cirrhosis)
- Amiodarone
- Arsenicals
- Oral contraceptives (Budd-Chiari)
- Pyrrolidizine alkaloids and antineoplastic agents (veno-occlusive disease)

Inherited and metabolic disorders
- Alpha-1 antitrypsin deficiency
- Wilson's disease
- Hemochromatosis
- Galactosemia
- Gaucher's disease
- Glycogen storage disease
- Cystic fibrosis

Biliary disorders
- Primary biliary cirrhosis
- Biliary atresia
- Primary sclerosing cholangitis
- Chronic biliary obstruction
- Progressive familial intrahepatic cholestasis

Cardiovascular causes
- Chronic right heart failure (cardiac cirrhosis)
- Budd-Chiari syndrome
- Long standing portal vein thrombosis

Others
- Nonalcoholic fatty liver disease (NASH)
- Sarcoidosis
- Scleroderma
- Autoimmune hepatitis
- Cryptogenic

Epidemiology

- Alcoholic cirrhosis is the most common type of cirrhosis seen all over the world. Post-hepatitic cirrhosis especially due to hepatitis B or C is the second most common cirrhosis.
- Cirrhosis is more common in males but primary biliary cirrhosis is more common in females.
- Cirrhosis is the most common indication for liver transplantation.

Pathology

- Cirrhosis is the final common pathway of many types of chronic liver injury.
- Irreversible chronic injury of the hepatic parenchyma leads to extensive fibrosis, loss of the normal liver architecture and formation of regenerative nodules. The changes in cirrhosis affect the whole liver. Destruction of the liver architecture causes distortion and loss of the normal hepatic vasculature with the development of portosystemic vascular shunts.
- Activation of the hepatic stellate cells is the central event leading to hepatic fibrosis. When activated, the quiescent fat-storing stellate cells become multifunctional cells, capable of collagen production, contraction and cytokine synthesis.
- Cirrhosis can be classified histologically into two types: (1) Micronodular cirrhosis is characterized by small nodules less than 3 mm in diameter, (2) Macronodular cirrhosis is characterized by larger nodules which are more than 3 mm in diameter. Differentiation between these morphologic types of cirrhosis has limited clinical value.

Clinical Features

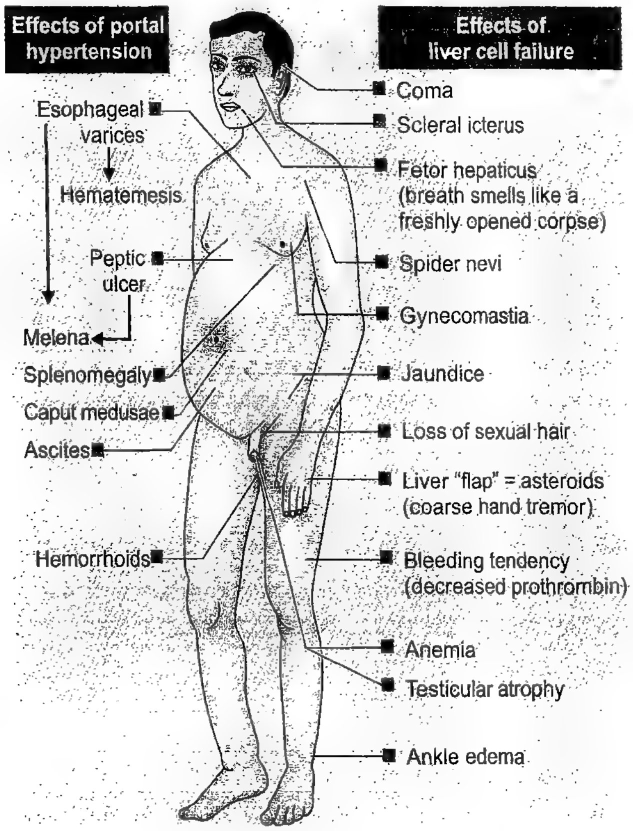

Fig. 7.3: Clinical features of cirrhosis of liver

Symptoms

- May be asymptomatic.
- Anorexia, weight loss, fatigue/weakness.
- Hematemesis, malena due to bleeding esophageal variceal bleeding.
- Abdominal distension due to ascites.
- Women may report menstrual irregularities due to endocrine alterations.

General Examination

- Muscle wasting
- Pallor due to GI blood loss

- Jaundice
- Spider angiomas
- Bleeding manifestations such as purpura, bruises
- Palmar erythema
- Pruritus
- Decreased body hair
- Gynecomastia
- Testicular atrophy
- Flapping tremors (in hepatic encephalopathy)
- Parotid gland enlargement
- Edema
- Clubbing may be present in primary biliary cirrhosis.
- Signs of virilization in women.

Abdomen

- Liver is shrunken, firm and nodular liver.
- Splenomegaly may be present.
- Ascites as evidenced by bulging flanks, shifting dullness and fluid thrill.
- Caput medusae (dilated veins around the umbilicus).
- *Melanosis*: Gradual darkening of the exposed areas of the skin.
- Steatorrhea.

CVS

Look for evidence of right heart failure (cardiac cirrhosis) such as raised JVP, right-sided S3, S4, dilated heart, etc.

RS

Pleural effusion (especially right sided) may develop in severe ascites.

NS

Patient can be in altered sensorium in hepatic encephalopathy, electrolyte imbalance, hypoglycemia, etc.

Investigations

Complete Blood Count

Anemia may be present due to blood loss, folate deficiency and hypersplenism. Pancytopenia due to hypersplenism.

Liver Function Tests

Hypoalbuminemia and increased globulin levels (reversal of A : G ratio). Bilirubin levels and aminotransferases may be mildly elevated. ALP is mildly elevated. Prothrombin time (PT) may be prolonged.

Table 7.3 Clues to specific etiology

Type of cirrhosis	Clues
• Alcoholic cirrhosis	History of prolonged or excessive alcohol consumption. Rule out other causes of cirrhosis since only 10–15% of individuals with excessive alcohol intake develop cirrhosis
• PBC (primary biliary cirrhosis)	Middle-aged women with unexplained pruritus or elevated ALP Positive serum antimitochondrial antibody liver biopsy should be performed to confirm diagnosis
• Secondary biliary cirrhosis	History of previous biliary tract surgery or gallstones. History of recurrent bouts of ascending cholangitis. History of right upper quadrant pain. Clinical and laboratory evidence of prolonged obstruction to bile flow. Ultrasound abdomen and cholangiography may demonstrate the underlying pathologic process.
• Post-hepatitic cirrhosis	Positive viral serology
• Cryptogenic cirrhosis	No identifiable cause of cirrhosis Liver biopsy also rules out any specific cause
• Cardiac cirrhosis	Signs and symptoms of heart failure usually overshadow liver disease Presence of firm, enlarged liver with signs of chronic liver disease in patients with valvular heart disease, constrictive pericarditis, or cor pulmonale of long duration (>10 years) should suggest cardiac cirrhosis
• Metabolic, hereditary, drug-related, and other types of cirrhosis	Specific history, clinical and lab features may be present Specific lab tests and liver biopsy required to confirm the diagnosis

Urea, Creatinine, Serum Electrolytes

- Urea and creatinine are usually normal unless there is development of hepatorenal syndrome.
- Metabolic disturbances such as hyponatremia, hypokalemia and hypoglycemia may be present. Hypoglycemia is due to impaired gluconeogenesis by the liver.

7

Investigations to Identify the Underlying Cause

- Hepatitis serologies (HBsAg, anti-HCV, anti-HDV).
- Iron, total iron-binding capacity and ferritin if hemochromatosis is suspected.
- Antimitochondrial antibody (AMA) if primary biliary cirrhosis is suspected.
- Antinuclear antibody, anti smooth-muscle antibody if autoimmune etiology is suspected.
- Serum copper and ceruloplasmin levels if Wilson disease is suspected.
- α_1-antitrypsin levels, if deficiency is suspected.

Imaging

- Abdominal ultrasound with Doppler may show nodular liver, splenomegaly and dilated portal vein with collateral vessels.
- CT or MRI is rarely required.

Liver Biopsy (Percutaneous, Transjugular, or Open)

This is the test for definitive diagnosis of cirrhosis but not routinely required except in cases of doubt about diagnosis and etiology. It shows regenerating nodules and fibrosis.

Treatment

- *Diet* should provide adequate calories and protein (1–1.5 g/kg/d). Reduce protein intake to 60–80 g/d if there is hepatic encephalopathy. Restrict sodium if there is fluid retention. Benefit of branched-chain amino acids to prevent or treat hepatic encephalopathy is uncertain. Vitamin supplementation is advisable especially vit K.
- All patients with cirrhosis should receive the HAV, HBV, and pneumococcal vaccines and a yearly influenza vaccine.
- Portal hypertension can be reduced by non-selective beta blockers such as propranolol or nadolol. Nitrates can be used for patients in whom beta blockers are contraindicated. Esophageal varices should be treated by endoscopic variceal ligation.
- Ascites and edema is treated by diuretics (spironolactone and frusemide). Correction of hypoalbuminemia by albumin transfusions also helps edema and ascites. Paracentesis is indicated for tense ascites. Transjugular intrahepatic portosystemic shunt (TIPS) is helpful in the treatment of severe refractory ascites.
- Lactulose syrup is used daily (15 ml at night) to prevent hepatic encephalopathy.
- Complications of cirrhosis such as hepatic encephalopathy and variceal bleed should be treated as per standard guidelines.
- Liver transplantation can be considered in suitable patients.

Prognosis

- The overall prognosis in cirrhosis is poor. Only 25% of patients survive 5 years from diagnosis. Prognosis is more favorable if the underlying cause can be corrected, such as alcohol abuse. Complications such as variceal bleed can cause unexpected death.
- *Indicators of poor prognosis in cirrhosis*: Presence of jaundice, ascites, encephalopathy, renal impairment, hyponatremia (<130 mEq/L), elevated hepatic venous pressure gradient, albumin <3 g/dl, bilirubin >3 mg/dl, cachexia, upper gastrointestinal bleeding.
- The Child-Pugh score is a tool to assess prognosis in cirrhosis.

Child-Turcotte-Pugh Scoring System to Assess the Severity of Liver Disease

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dl	<2	2–3	>3
Albumin, g/dl	>3.5	2.8–3.5	<2.8
Prothrombin time			
Second over control	<4	4–6	>6
OR INR	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

- A total score of 5–6 is considered grade A (well-compensated disease).
- Score 7–9 is grade B (significant functional compromise).
- Score 10–15 is grade C (decompensated disease).
- These grades correlate with one- and two-year patient survival: grade A—100 and 85%; grade B—80 and 60%; and grade C—45 and 35%.

Complications

- Portal HTN
- Variceal bleeding
- Spontaneous bacterial peritonitis
- Hepatic encephalopathy
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Hepatocellular carcinoma.

Q. What is biliary cirrhosis? Discuss the etiology, pathology, clinical features, investigations, and management of primary biliary cirrhosis.

Q. Secondary biliary cirrhosis.

- Biliary cirrhosis is cirrhosis of liver due to injury or prolonged obstruction of intrahepatic or extrahepatic biliary system.
- It is associated with impaired biliary excretion, destruction of liver parenchyma, and progressive fibrosis.
- Biliary cirrhosis can be divided into 2 types:
  - *Primary biliary cirrhosis (PBC)*: Here cirrhosis is due to chronic inflammation and fibrous obliteration of intrahepatic bile ductules.
  - *Secondary biliary cirrhosis (SBC)*: Here cirrhosis is due to prolonged obstruction of extrahepatic bile ducts.
- Although PBC and SBC are separate entities, many clinical features are similar.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is liver cirrhosis due to chronic inflammation and fibrous obliteration of intrahepatic bile ductules.

Epidemiology

- PBC is common in Europe and America but is rare in Africa and Asia.
- Females are affected more commonly (female to male ratio 9 : 1).
- It is also more common amongst cigarette smokers.

Etiology and Pathology

- Its cause is unknown but probably an autoimmune disorder because it is associated with other autoimmune disorders such as sicca syndrome, autoimmune thyroiditis, type 1 diabetes, etc.
- The condition is strongly associated with the presence of antimitochondrial antibodies (AMA), which are diagnostic. Antinuclear antibodies (ANA) are also positive in these cases.
- The main pathology is chronic granulomatous inflammation of the portal tracts, which destroys small and middle-sized intrahepatic bile ducts. This in turn, leads to fibrosis and cirrhosis of liver.

Clinical Features

- Most patients are women.
- Many patients are asymptomatic for years.
- The condition typically presents with an insidious onset of itching and/or tiredness. Itching may precede jaundice by months or years. Over a period of months to years, itching and jaundice worsen.
- As cirrhosis develops, signs of hepatocellular failure and portal hypertension develop and ascites appears.
- Steatorrhea can occur due to impaired fat absorption due to impaired bile excretion into the duodenum. There is malabsorption of fat-soluble vitamins such as vit D leading to osteomalacia or osteoporosis causing bone pain or fractures (hepatic osteodystrophy).
- Impaired excretion of cholesterol through bile leads to elevation of serum cholesterol and subcutaneous lipid deposition around the eyes (xanthelasmas) and over joints and tendons (xanthomas).
- Physical examination may reveal scratch marks on the skin due to itching, hyperpigmentation, xanthelasmas and xanthomas, hepatomegaly, splenomegaly, and clubbing of the fingers.

Investigations

- LFTs show a cholestatic pattern. There is elevation of the serum ALP (alkaline phosphatase). Serum 5′-nucleotidase activity and γ-glutamyl transpeptidase levels are also elevated. Serum bilirubin is usually normal and aminotransferase levels are minimally increased.
- Hypercholesterolemia is common
- The antimitochondrial antibody is present in most patients
- Ultrasound abdomen shows normal extrahepatic biliary ducts.
- Liver biopsy is only necessary if there is diagnostic uncertainty.

Treatment

- There is no specific treatment for PBC.
- Ursodeoxycholic acid (UDCA) has been shown to improve biochemical markers of cholestasis and jaundice. It also slows disease progression but does not change the final outcome. The hydrophilic UDCA improves bile flow, replaces toxic hydrophobic bile acids in the bile acid pool, and reduces apoptosis of the biliary epithelium. UDCA should be given in doses of 13 to 15 mg/kg per day.
- Immunosuppressants such as corticosteroids, azathioprine, penicillamine and ciclosporin have all been tried in PBC but none is effective.
- Relief of symptoms: Itching can be controlled by UDCA and cholestyramine (an oral bile salt-sequestering resin). Other drugs helpful for itching are rifampicin, opiate antagonists (naloxone or naltrexone), ondansetron, and ultraviolet light. Steatorrhea can be reduced by a low-fat diet and substituting medium-chain triglycerides for dietary long-chain triglycerides. Fat-soluble vitamins A, D, E, and K should be supplemented. Patients should be screened periodically for osteoporosis and osteomalacia by bone densitometry and treated as needed with calcium supplements, vitamin D and/or bisphosphonate agents (e.g. alendronate) if osteoporosis is present.

- Liver transplantation is the only treatment which offers a cure for PBC. It should be considered in liver failure and intractable pruritus. Recurrence of PBC after liver transplantation is rare.

Secondary Biliary Cirrhosis

- This is cirrhosis of liver due to prolonged obstruction of extrahepatic bile ducts.
- Obstruction may be due to gallstones, benign bile duct strictures or sclerosing cholangitis. Carcinomas rarely cause secondary biliary cirrhosis because patients die before cirrhosis develops.
- Clinical features and biochemical findings are same as primary biliary cirrhosis. In addition, there may be recurrent episodes of cholangitis associated with fever and right upper quadrant pain. Cholangitis requires treatment with antibiotics, which can be given continuously if attacks recur frequently.
- Ultrasound abdomen and cholangiography (PTC or ERCP) can identify the site and cause of obstruction.
- Treatment involves relief of obstruction to bile flow, by either endoscopic or surgical means. Antibiotics should be given for episodes of cholangitis.

Q. Cardiac cirrhosis.

Definition

Cardiac cirrhosis is cirrhosis of liver due to prolonged, severe right-sided congestive heart failure. Other cardiac disorders which can produce cirrhosis are valvular heart disease and constrictive pericarditis.

Pathogenesis

- Right-sided heart failure leads to retrograde transmission of elevated venous pressure and congestion of the liver. Hepatic sinusoids become dilated and the liver becomes tensely swollen.
- Prolonged passive congestion and ischemia from reduced cardiac output leads to necrosis of centrilobular hepatocytes and fibrosis. Ultimately extensive fibrosis leads to cirrhosis.
- Gross examination of the liver shows alternating red (congested) and pale (fibrotic) areas, a pattern referred to as "nutmeg liver."

Clinical Features

- Features of heart failure are more prominent than cirrhosis. Patients complain of dyspnea, orthopnea, and PND. Signs of congestive cardiac failure such as raised JVP, lung crepitations, S3 gallop, tricuspid regurgitation murmur, peripheral edema and enlarged heart are usually present.
- Hepatomegaly is common. Other features of cirrhosis may be present.

Investigations

- LFTs are similar to other causes of cirrhosis.
- ECG and echocardiogram show features of right heart failure or other cardiac disease.

Treatment

- Underlying cardiac disorder must be treated. Mainstay of treatment is diuretics. Loop diuretics (furosemide) or spironolactone can be used.
- Treatment of cirrhosis is same as other types of cirrhosis (*see* cirrhosis).

Q. Gynecomastia.

- Gynecomastia is defined as a benign proliferation of the glandular tissue of the male breast.
- It presents clinically as the presence of a rubbery or firm mass extending concentrically from the nipple.
- Fat deposition without glandular proliferation is termed pseudogynecomastia. Pseudogynecomastia is seen in obese men.

Causes of Gynecomastia

- Puberty (physiologic gynecomastia)
- Testicular neoplasms (due to production of HCG)
- Feminizing adrenocortical tumors
- Ectopic production of human chorionic gonadotropin
- Male hypogonadism
- Enzymatic defects of testosterone production
- Androgen-insensitivity syndromes
- True hermaphroditism
- Cirrhosis of liver
- Starvation, during the recovery phase
- Chronic renal failure on hemodialysis
- Hyperthyroidism
- Excessive extraglandular aromatase activity
- Drugs (spironolactone, ketoconazole)
- Idiopathic

History

- Ask about the duration of breast enlargement, pain, nipple discharge, whether secondary sexual characteristics are fully developed, and the relationship between onset of gynecomastia and puberty.
- H/o delayed puberty, decreased libido, and erectile dysfunction suggests hypogonadism.
- H/o chronic alcohol intake, jaundice and ascites suggest cirrhosis of liver. H/o tremor, heat intolerance, and diarrhea suggest hyperthyroidism.

- Enquire about the drug intake which can cause gynecomastia.

Physical Examination

- Look for development of secondary sexual characteristics (e.g. the penis, pubic hair, and axillary hair). Also look for development of mustache and beard. Non-development of these features suggests hypogonadism. Examine the testes for masses or atrophy.
- Examine the breasts for any nipple discharge, consistency, fixation to underlying tissues, and skin changes. Findings which suggest malignancy are eccentric breast swelling, nipple discharge, fixation to the skin, nipple retraction, axillary lymphadenopathy, and hard consistency.
- Look for signs/symptoms of hypogonadism such as absence of pubic hair, testicular atrophy, infantile penis, etc.
- Look for symptoms or signs of hyperthyroidism (e.g. tremor, tachycardia, sweating, heat intolerance, weight loss).

Investigations

- Mammography is done if breast cancer is suspected.
- If hypogonadism is suspected, serum LH, FSH, testosterone, estradiol, and HCG levels should be measured.
- Further tests are based on the suspicion of underlying disease.

Treatment

- No specific treatment is needed for physiological gynecomastia which usually remits spontaneously.
- Treatment of the underlying cause.
- Drugs causing gynecomastia should be stopped.
- Tamoxifen 10 mg orally bid can be tried if pain and tenderness are very troublesome.
- If cosmetic appearance is unacceptable, surgical removal of excess breast tissue can be done.

Q. Describe the anatomy of the portal venous system. How do you define and classify portal hypertension?

Q. Discuss the etiology, pathology, clinical features, investigations, complications and management of portal hypertension.

Definition

Portal hypertension is chronic elevation of the portal venous pressure more than 10 mm Hg or 15 cm of saline (normal, 5–10 mm Hg or 10–15 cm of saline).

Anatomy of the Portal Venous System

- The portal vein is formed by the union of the superior mesenteric vein and the splenic vein.

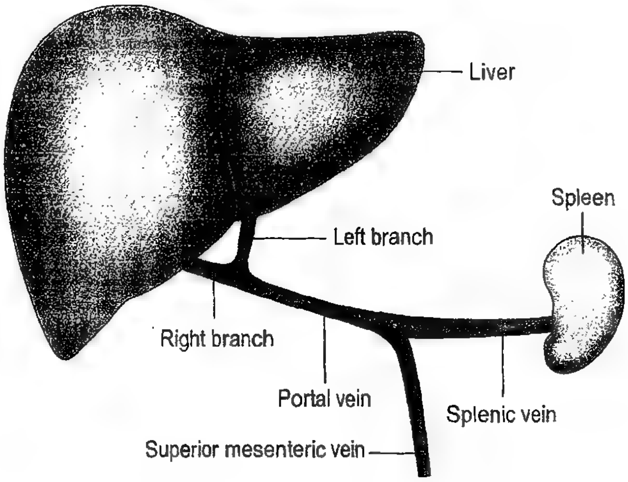

Fig. 7.4: Anatomy of the portal venous system

- Portal vein divides into right and left branches at the hepatic hilum which further divide into segmental branches. These end up into hepatic sinusoids. From sinusoids, blood drains into hepatic veins (right, left and middle) and then into the inferior vena cava (IVC).
- The portal venous system drains blood from the entire gastrointestinal (GI) tract starting from the esophagogastric junction down to the upper one-third of the rectum, spleen and pancreas. The veins of the portal system are valveless.

Etiology

Prehepatic

- Portal vein obstruction (e.g. portal vein thrombosis)
- Increased blood flow through portal vein (splanchnic arteriovenous fistula, massive splenomegaly)

Intrahepatic

- Cirrhosis
- Drug toxicity (e.g. vinyl chloride, arsenic, vitamin A, 6-mercaptopurine)
- Malignant or metastatic hepatic diseases
- Myeloproliferative diseases
- Nodular regenerative hyperplasia
- Sarcoidosis
- Schistosomiasis
- Wilson's disease

Posthepatic

- Hepatic vein thrombosis (Budd-Chiari syndrome)
- Cardiac disease (e.g. constrictive pericarditis, cardiomyopathy)
- Inferior vena cava obstruction

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Pathology

- Portal venous pressure depends on portal blood flow and portal vascular resistance. Increased vascular resistance is the main cause of portal hypertension.
- Increased portal vascular resistance leads to decreased portal blood flow to the liver and development of collateral vessels, allowing portal blood to bypass the liver and enter the systemic circulation directly (portosystemic shunting).
- Collateral vessels are seen in the esophagus, stomach, rectum, anterior abdominal wall, and in the renal, lumbar, ovarian and testicular vasculature. As collateral vessel formation progresses, more and more portosystemic shunting takes place.
- Dilatation of collateral vessels in the lower end of esophagus leads to varices.
- Increased portal pressure leads to congestion of the spleen and splenomegaly.
- Rarely increased blood flow through portal vein can cause portal HTN (e.g. massive splenomegaly from which there is high blood flow into the portal vein).

Clinical Features

- The clinical features of portal hypertension result mainly from portal venous congestion and collateral vessel formation.
- Splenomegaly is present usually (mild to moderate). If splenomegaly is absent, diagnosis of portal hypertension is unlikely. Splenomegaly results in hypersplenism which can cause thrombocytopenia or even pancytopenia.
- Dilated veins may be seen on the anterior abdominal wall. Dilated veins radiating from the umbilicus are called caput medusae. Venous hum may be heard over a large umbilical collateral vein (Cruveilhier-Baumgarten syndrome).
- Dilated veins in the esophagus and stomach (gastroesophageal varices) can bleed and cause hematemesis and melena.
- Rectal varices can also cause bleeding and are often mistaken for hemorrhoids.
- Fetor hepaticus results from portosystemic shunting of blood, which allows mercaptans to pass directly to the lungs.
- Severe portal HTN can lead to ascites.

Investigations

- *Blood tests*: Anemia may be present due to hypersplenism and bleeding varices. Liver function tests are usually normal in patients with non-cirrhotic portal hypertension but may be altered in cirrhosis.
- *Endoscopy*: Upper GI endoscopy shows gastroesophageal varices.
- *Ultrasonography*: Ultrasonography (USG) of the liver and portal venous system helps to establish the diagnosis of portal HTN. It shows dilated collaterals around the gastroesophageal junction and splenic hilum, splenomegaly, and dilated portal vein and splenic vein. It can also help in diagnosing the cause of portal HTN such as cirrhosis, portal vein thrombosis, etc. Doppler USG can assess the direction and velocity of blood flow in the portal vein.
- *Liver biopsy* is indicated in selected cases to diagnose the cause of portal HTN.
- *Portal venography*: Demonstrates the site and often the cause of portal venous obstruction and is performed prior to surgical intervention.

Complications of Portal Hypertension

- Variceal bleeding
- Congestive gastropathy
- Hypersplenism
- Ascites
- Renal failure
- Hepatic encephalopathy

Treatment

Reduction of Portal Pressure

- Nonselective beta blockers such as propranolol or nadolol reduce portal pressure through splanchnic vasoconstriction and reduced cardiac output. Drugs should be titrated to a target pulse rate of 60/min or reduction of resting pulse by 25%. Nitrates (isosorbide mononitrate and dinitrate) can be used if beta blockers are contraindicated.
- Portosystemic shunt surgeries such as portocaval shunt, splenorenal shunt, etc. are done less commonly now with the availability of TIPS (transjugular intrahepatic portosystemic stent).
- TIPS: Here, a portal-systemic shunt is placed through internal jugular vein percutaneously. It decompresses the portal circulation.
- Wherever possible, underlying cause of portal HTN should be treated.
- Liver transplantation is helpful in selected patients.

Treatment of Complications

Complications such as variceal bleed, encephalopathy, ascites, etc. should be treated as per standard guidelines.

Q. Discuss the diagnosis, differential diagnosis, and management of acute variceal bleeding.

Q. Transjugular intrahepatic portosystemic stent (TIPS).

- Variceal bleeding occurs from esophageal varices that are usually located within 3–5 cm of the esophagogastric junction, or from gastric varices.
- Higher grade of varices (grades 3 and 4), red spots and red stripes, high portal pressure and liver failure, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are associated with increased risk of variceal bleeding.
- Variceal bleeding can be severe and mortality from bleeding esophageal varices is high (up to 50% in those with advanced liver disease).

Diagnosis of Variceal Bleed

- *Hematemesis*: Vomiting of fresh or altered blood ("coffee grounds" appearance).
- *Melena*: Altered (black) blood passed by rectum.
- Hyperactive bowel sounds and an elevated blood urea (due to volume depletion and blood proteins absorbed in the small intestine) and low hemoglobin suggest upper GI bleeding.
- *Hemodynamic changes*: Significant variceal bleed may lead pallor, tachypnea, tachycardia, and hypotension.
- Nasogastric tube lavage reveals fresh or altered blood in the stomach.
- Upper GI scopy can confirm the diagnosis.

Differential Diagnosis of Variceal Bleed

- Peptic ulcer
- Mallory-Weiss tears
- Gastroduodenal erosions
- Erosive esophagitis
- Cancer
- Aortoenteric fistulae
- Vascular lesions

Management of Acute Variceal Bleeding

- Variceal bleeding is a life-threatening emergency. Patients should be admitted to an intensive care unit. Blood pressure, pulse rate, urine output, and mental status should be monitored.
- Intravascular volume replacement should be done with IV fluids and blood transfusion.
- Replacement of clotting factors with fresh-frozen plasma is important in patients with coagulopathy.
- The measures used to control acute variceal bleeding include endoscopic therapy (banding or sclerotherapy), balloon tamponade, esophageal transection, TIPS and splanchnic vasoconstrictors.

Variceal Banding

This is the treatment of choice in acute variceal bleeding. It stops variceal bleeding in 80% of patients and can be repeated if bleeding recurs. This is a technique in which varices are sucked into an endoscope accessory, and occluded with a tight rubber band. The occluded varix subsequently sloughs with variceal obliteration. It should be repeated at regular intervals to obliterate all varices. Banding is more effective than sclerotherapy, with fewer side effects and is the treatment of choice.

Sclerotherapy

In this technique, varices are injected with a sclerosing agent to obliterate them. It is less preffered now because of the availability of band ligation. Sclerotherapy can cause transient dysphagia, chest pain, esophageal perforation and esophageal strictures.

Splanchnic Vasoconstrictors

- Terlipressin and octreotide reduce the portal pressure and can stop variceal bleeding. Terlipressin dose is 2 mg IV 6-hourly until bleeding stops and then 1 mg 6-hourly for a further 24 hours.
- Octreotide is given as 50 μg IV bolus followed by an infusion of 50 μg per hour.

Balloon Tamponade

- This technique employs a Sengstaken-Blakemore tube with two balloons which exert pressure in the fundus of the stomach and in the lower esophagus respectively when inflated.
- The tube is passed through the mouth into the stomach and gastric balloon is inflated with 200–250 ml of air, which controls gastric variceal bleed. Then esophageal balloon is inflated to compress the esophageal varices.
- Pressure in the esophageal balloon should be monitored with a sphygmomanometer and should not exceed 40 mm Hg.
- Balloon tamponade will almost always stop esophageal and gastric fundal variceal bleeding, but this is only a temporary measure. Definitive therapy such as banding or sclerotherapy should be arranged as early as possible.

TIPS

- TIPS can be used for acute bleeding not responding to sclerotherapy or banding.

- This technique involves placing a stent between portal and hepatic vein in the liver to reduce portal pressure. It is done under radiological guidance via the internal jugular vein. Patency of the portal vein must be confirmed before the procedure by angiography. Any coagulation defect should be corrected by fresh frozen plasma, and prophylactic antibiotics are given. Successful shunt placement stops and prevents variceal bleeding.
- Shunt narrowing or occlusion can happen which can cause rebleeding from varices. It can be corrected by angioplasty.
- Although TIPS is better than endoscopic therapy in preventing rebleeding, survival is not improved. There is a higher risk of hepatic encephalopathy with TIPS since the portal blood is shunted directly into systemic circulation.

Esophageal Transection

- This operation is used when other measures cannot control variceal bleeding and transjugular intrahepatic portosystemic stenting (TIPS) is not available.
- Transection of the varices can be done with a stapling gun but the procedure carries significant operative morbidity and mortality.

Shunt Surgery

- Emergency portosystemic shunt surgery has a mortality of 50% or more and is done rarely now.
- Portosystemic shunts are now reserved for patients in whom all other treatments have failed.
- Non-selective portacaval shunts can divert majority of the portal blood away from liver, leading to a high risk of postoperative liver failure and hepatic encephalopathy. Selective shunts (such as the distal splenorenal shunt) are associated with less encephalopathy. Survival is not prolonged by shunt surgeries.

Prevention of Recurrent Bleeding

- Recurrent bleeding happens in almost all the patients who have bleed previously. Hence, following preventive measures are needed.
- Band ligation
- Sclerotherapy
- Portosystemic shunt surgery
- *Beta-adrenoceptor antagonists*: Propranolol or nadolol reduce portal venous pressure and prevent recurrent variceal bleeding.

Q. List the drugs used to reduce portal venous pressure.

Splanchnic vasoconstrictors
- Vasopressin
- Terlipressin
- Somatostatin
- Octreotide

Non-selective beta blockers
- Propranolol
- Nadolol

Nitrates

Isosorbide mononitrate and dinitrate

Q. Define hepatic encephalopathy (porto-systemic encephalopathy or hepatic coma). Discuss the pathogenesis, clinical features, investigations, and treatment of hepatic encephalopathy.

- Hepatic encephalopathy (HE) is a reversible neuro-psychiatric syndrome occurring in patients with advanced liver failure.
- Its severity ranges from inversion of sleep rhythm and mild intellectual impairment to coma.

Pathogenesis

- Hepatic encephalopathy is thought to be due to a biochemical disturbance of brain function.
- It happens due to some biochemical 'neurotoxins' (ammonia, aminobutyric acid, amino acids, mercaptans and fatty acids) produced in the gut, which are normally metabolized by the healthy liver. In the presence of liver failure and portosystemic shunting these nitrogenous substances enter systemic circulation and brain. Ammonia is the most important of these and it has multiple neurotoxic effects. It can alter the transit of amino acids, water, and electrolytes across astrocytes and neurons. It can impair amino acid metabolism and energy utilization in the brain. Ammonia can also inhibit the generation of excitatory and inhibitory postsynaptic potentials.
- Disruption of the blood–brain barrier is a feature of acute hepatic failure and may lead to cerebral edema and encephalopathy.
- Precipitating factors for hepatic encephalopathy.
  - Bleeding into the intestinal tract increases the amount of protein in the bowel and precipitates encephalopathy.
  - Other precipitants include constipation, alkalosis, hypokalemia, sedatives, large volume ascitic tap, infection, and portosystemic shunts (including TIPS).

Clinical Features

- Early hepatic encephalopathy may not be clinically recognizable except for mild cognitive, psychomotor, and attention deficit on standardized tests.
- Alteration of sleep cycle characterized by day time sleepiness and night time insomnia is an early symptom (inversion of sleep rhythm).
- As the severity of hepatic encephalopathy increases, it leads to confusion, restlessness, drowsiness, disorientation, stupor, and finally coma. Convulsions can sometimes occur.
- Examination usually shows a flapping tremor (asterixis), inability to perform simple mental arithmetic calculations and draw objects such as a star (constructional apraxia). As the condition progresses, hyper-reflexia and bilateral extensor plantar responses may be seen.
- Focal neurological signs may be rarely present in hepatic encephalopathy. However, other causes such as stroke should be ruled out in such patients.
- Signs of liver cell failure such as fetor hepaticus (sweet musty odor to the breath due to the presence of mercaptans), jaundice, spider nevi, coagulation defect, disturbances, etc. may be present.

Clinical grading of hepatic encephalopathy

Grade 1: Euphoria or depression, mild confusion, slurred speech, disordered sleep rhythm
Grade 2: Lethargy, moderate confusion
Grade 3: Marked confusion, incoherent speech, sleeping but arousable
Grade 4: Coma; initially responsive to noxious stimuli, later unresponsive
Flaps are present in grades 2 and 3, and absent in grades 1 and 4 hepatic encephalopathy.

Differential Diagnosis of Hepatic Encephalopathy

- Subdural hematoma
- Drug or alcohol intoxication
- Delirium tremens
- Wernicke's encephalopathy
- Primary psychiatric disorders
- Hypoglycemia
- Neurological problems
- Wilson's disease.

Investigations

- Diagnosis is made by clinical features. However, following tests may be helpful in doubtful situations.
- Serum ammonia levels are increased. But the severity of hepatic encephalopathy does not correlate with ammonia levels.
- Electroencephalogram (EEG) shows diffuse slowing of the normal alpha waves with eventual development of delta waves.
- Serum electrolytes, urea, creatinine, glucose, etc. should be done to rule out other causes of altered sensorium.
- Brain imaging (CT or MRI) is required if stroke is suspected.

Treatment

- Lactulose is given orally, initially at a dose of 30 ml three or four times daily. The dose should then be titrated so that two or three soft stools per day are produced. Lactulose is a nonabsorbable synthetic disaccharide. It is digested by bacteria in the colon to short-chain fatty acids, resulting in acidification of colon contents. This acidification favors the formation of ammonium ion (NH_4^+) from ammonia. Ammonium is not absorbable, and excreted in the stools. Lactulose also inhibits intestinal bacteria by formation of acidic environment which decreases ammonia production by bacteria. Lactulose can also be given rectally as retention enema.
- Rifaximin 400 mg three times daily controls ammonia-producing intestinal bacteria. Alternative antibiotics are metronidazole, neomycin and vancomycin.
- Flumazenil (benzodiazepine antagonist) is effective in some patients with severe hepatic encephalopathy.
- Opioids and sedatives should be avoided. Oxazepam can be given to control agitation as it is not metabolized by the liver.
- Dietary protein should be restricted. Vegetable protein is better tolerated than meat protein. Gastrointestinal bleeding should be controlled and blood should be purged from the gastrointestinal tract. This can be done by nasogastric aspiration and by giving lactulose to induce diarrhea.
- Chronic or refractory hepatic encephalopathy requires liver transplantation.

Q. Hepatorenal syndrome.

Definition

- The hepatorenal syndrome refers to the development of acute renal failure in a patient who has advanced liver disease, in the absence of identifiable specific causes of renal dysfunction.
- Hepatorenal syndrome is diagnosed only when other causes of renal failure (including prerenal azotemia and acute tubular necrosis) have been excluded.

Pathogenesis

The exact cause of this syndrome is not clear, but altered renal hemodynamics appears to be involved. There is intense renal vasoconstriction, perhaps in response to the splanchnic vasodilation accompanying cirrhosis. Kidneys are histologically normal. If these kidneys are transplanted to people without liver disease, they function normally.

Clinical Features

- Worsening azotemia.
- Hyponatremia.
- Progressive oliguria.
- Hypotension.
- It is often precipitated by severe gastrointestinal bleeding, sepsis, or vigorous diuresis or paracentesis.
- Based upon the speed of onset of renal failure, two forms of hepatorenal syndrome have been recognized. Type I hepatorenal syndrome is characterized by progressive oliguria, a rapid rise of the serum creatinine and a very poor prognosis (without treatment median survival is less than 1 month). Type II hepatorenal syndrome is more slowly progressive and chronic.

Criteria for the diagnosis of hepatorenal syndrome

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
- A plasma creatinine concentration above 1.5 mg/dl that progresses over days to weeks.
- The absence of any other apparent cause for the renal disease, including shock, ongoing bacterial infection, current or recent treatment with nephrotoxic drugs, and the absence of ultrasonographic evidence of obstruction or parenchymal renal disease.
- A urine sodium concentration below 10 mEq/L (off diuretics), a urine osmolality above that of the plasma, and protein excretion less than 500 mg/day.
- Lack of improvement in renal function after volume expansion with 1.5 liters of isotonic saline, and if pertinent, withdrawal of diuretics.

Treatment

- There is no effective treatment for hepatorenal syndrome so far.
- Intravenous albumin infusion may help in some cases.
- Splanchnic vasoconstrictors such as terlipressin, and octreotide can be tried and have shown benefit.
- Prolongation of survival has been associated with use of the molecular adsorbent recirculating system (MARS), a modified dialysis method that selectively removes albumin-bound substances.
- TIPS has been reported to improve renal function in some patients but its use cannot be universally recommended.
- Liver transplantation is the treatment of choice for hepatorenal syndrome.

Q. Define ascites. Discuss the causes and approach to a case of ascites.

Q. Discuss the etiology, clinical features, investigations and management of a case of ascites.

Q. Puddle sign.

Ascites refers to the accumulation of excess fluid in the peritoneal cavity.

Causes of Ascites

- Cirrhosis with portal HTN
- Cardiac failure
- Renal failure
- Hypoproteinemia (nephrotic syndrome, protein-losing enteropathy, malnutrition)
- Intra-abdominal malignancy
- Pancreatitis
- Abdominal tuberculosis
- Hepatic venous occlusion (Budd-Chiari syndrome, veno-occlusive disease)
- Rare causes (Meigs' syndrome, lymphatic obstruction, vasculitis, hypothyroidism)

Clinical Features

Symptoms

- Abdominal distension.
- Dyspnea and orthopnea due to pushed up diaphragm.
- Epigastric and retrosternal burning sensation due to gastro-esophageal reflux due to increased intra-abdominal pressure.
- Low grade fever and weight loss suggests tuberculous etiology.
- Presence of exertional dyspnea, orthopnea and PND suggests heart failure.

Signs

- At least 1 liter fluid should be present to be clinically detectable.
- Presence of jaundice and dilated veins over the abdomen indicate cirrhosis of liver with portal HTN. Other stigmata of live disease such as spider nevi, palmar erythema, gynecomastia, etc. may be present.
- Diffuse abdominal distension with fullness in the flanks. Skin appears shiny.
- Umbilicus is flush with the skin or everted.
- Shifting dullness present on percussion. Horseshoe shaped dullness is present in supine position.

- Fluid thrill is present in tense ascites.
- *Puddle sign*: This is useful to detect even minimal ascites (as low as 120 ml). Patient is put in prone position for 5 minutes. Then he is put in knee elbow postion. Diaphragm of stethoscope is applied to the most dependent part of the abdomen. One flank is flicked with a finger repeatedly while auscultating. Move the diaphragm gradually to opposite flank. A change in percussion note indicates presence of fluid.
- Tenderness may be present in the abdomen and points towards an infectious etiology such as tuberculosis or peritonitis.
- Herniae, abdominal striae, divarication of the recti and scrotal edema may be present.
- Pleural effusions may be present in some patients usually on the right side.
- In cases of ascites due to heart failure, signs of congestive heart failure such as raised JVP, basal lung crepitations and third heart sound may be present.
- In cases of malignant ascites, sometimes a mass may be palpable per abdomen.

Investigations

Ultrasound Abdomen

This is the easiest and most sensitive test to detect ascites. It can also show the underlying cause of ascites in many cases such as cirrhosis of liver, intra-abdominal malignancy, portal HTN, etc.

Ascitic Fluid Analysis

- *Appearance*: Clear or straw-colored in case of transudates. Turbid appearance is seen in infections and malignancy. White color appearance is seen in chylous ascites. Dark brown color indicates biliary tract perforation. Black fluid may indicate the presence of pancreatic necrosis or metastatic melanoma.
- *Cell count*: Normal ascitic fluid contains fewer than 500 WBCs/μl and fewer than 250 polymorphonuclear leukocytes (PMNs)/μl. High WBC count is found in infections. A PMN count of greater than 250 cells/μl is highly suggestive of bacterial peritonitis. Presence of high percentage of lymphocytes indicates tuberculous etiology.
- *SAAG*: The SAAG is the best single test for classifying ascites into transudative (SAAG >1.1 g/dl) and exudative (SAAG < 1.1 g/dl) causes. It is calculated by subtracting the ascitic fluid albumin value from the serum albumin value.
- *Total protein*: Total ascitic fluid protein greater than or equal to 2.5 g/dl indicates exudative ascites. An elevated SAAG and a high protein level are observed in most cases of ascites due to hepatic congestion. The combination of a low SAAG and a high protein level is characteristic of malignant ascites.
- *Culture/Gram stain/AFB stain*: These are useful to identify the infecting organism in cases of ascites due to intraabdominal infections.
- *Malignant cytology*: Useful in cases of suspected malignant ascites.
- *Ascitic fluid amylase* is typically >1000 mg/dl in pancreatic ascites.
- *Adenosine deaminase (ADA)* is usally more than 40 U/l in tuberculous ascites.

Chest X-ray

Pleural effusion may be present in cases of massive ascites.

CT Abdomen

- Useful to diagnose or rule out cirrhosis, malignancy, tuberculosis, etc.

ECG/Echocardiogram

To rule out congestive cardiac failure.

Treatment

- Treat the underlying cause.
- Sodium restriction (20 to 30 mEq/d) and diuretic therapy in cases of transudative ascites.
- Therapeutic paracentesis may be performed in patients who require rapid symptomatic relief for refractory or tense ascites.
- The transjugular intrahepatic portosystemic shunt (TIPS) is useful in cirrhotic patients with refractory ascites.

Q. Discuss the pathogenesis and management of ascites in cirrhosis.

Pathogenesis of Ascites in Cirrhosis

- The accumulation of ascitic fluid represents a state of total-body sodium and water excess. The exact cause of ascites formation is not understood, but most likely it is multifactorial. The following mechanisms may play a role.
- *Renal retention of sodium and water*: Cirrhosis of liver leads to accumulation of nitric oxide which causes splanchnic and peripheral arterial dilatation leading to a decrease in effective circulating blood volume. This apparent decrease in intravascular volume (underfilling) is sensed by the kidney, leading to activation of renin-angiotensin system with secondary hyperaldosteronism, increased sympathetic activity, and increased atrial

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natriuretic hormone secretion. All these changes lead to salt and water retention.

- *Increased hydrostatic pressure in portal venous system*: Splanchnic vasodilatation also leads to increased portal venous blood flow. This combined effect of increased portal blood flow and portal HTN leads to increased hydrostatic pressure in portal circulation leading to oozing out of fluid from capillaries into the peritoneum.
- *Hypoalbuminemia*: Decreased serum albumin in cirrhosis leads to decreased oncotic pressure in the splanchnic circulation and ascites formation.

Investigations

Ascitic Fluid Analysis

- Ascitic fluid is clear or straw-colored in cirrhosis. It is usually transudate unless complicated by SBP. Cell count is less than 250.
- The ascites protein concentration and the serum-ascites albumin gradient (SAAG ratio) is used to distinguish ascites due to transudation from ascites due to exudation. Cirrhotic patients usually have transudate with a SAAG ratio of >1.1.

Ultrasound Abdomen

- It confirms the diagnosis especially when small amounts are present.
- Ultrasound abdomen can also point towards the underlying cause of ascites such as cirrhosis, pancreatitis, etc.

Treatment

- *Salt restriction*: 2 gm per day.
- *Fluid restriction*: 1 liter /day.
- *Diuretics:* Spironolactone is the initial drug of choice (50–400 mg/d). Furosemide (40–160 mg/d) can be added if not responding to spironolactone alone. Spironolactone can cause painful gynecomastia and hyperkalemia. Diuresis is improved if patients are rested in bed while the diuretics are acting, perhaps because renal blood flow increases in the horizontal position.
- *Paracentesis*: Therapeutic paracentesis is done in severe ascites. Albumin infusion should be given during large volume paracentesis. This should be followed by maintenance diuretic therapy and sodium restriction.
- *Shunts*: Portacaval shunt, peritoneovenous shunt and TIPS can reduce ascites but do not improve life expectancy.

Q. Refractory ascites.

Patients who do not respond to doses of 400 mg spironolactone and 160 mg furosemide are considered to have refractory or diuretic-resistant ascites.

Differential Diagnosis of Refractory Ascites

- Malignant ascites
- Nephrogenic ascites (end-stage renal disease)
- Budd-Chiari syndrome (hepatic vein thrombosis)

Treatment Options

- Liver transplantation
- Serial therapeutic paracentesis
- Colloid replacement
- Extracorporeal ultrafiltration and reinfusion
- Transjugular intrahepatic portosystemic stent/shunt (TIPS)
- Peritoneovenous shunt
- Surgical portosystemic shunts

Q. Spontaneous bacterial peritonitis (SBP).

- Spontaneous bacterial peritonitis (SBP) is defined as an ascitic fluid infection without an evident intra-abdominal surgically treatable source. Patients with cirrhosis are very susceptible to infection of ascitic fluid.
- The source of infection cannot usually be determined, but most organisms isolated from ascitic fluid or blood cultures are of enteric origin and *Escherichia coli* is the organism most frequently found.

Clinical Features

- Abdominal pain, rebound tenderness, absent bowel sounds and fever in a patient with obvious features of cirrhosis and ascites.
- Abdominal signs are mild or absent in about one-third of patients, and in these patients hepatic encephalopathy and fever are the main features.
- Hypotension and hypothermia suggests advanced infection and such patients usually do not survive.

Investigations

- Blood count shows leukocytosis.
- *Ascitic fluid analysis*: Cloudy fluid, total leukocyte counts is >500/mm^3 and neutrophil count is >250/mm^3.
- Ascitic fluid Gram stain and culture can identify the organism which is usually *E. coli*.
- Finding of multiple organisms on culture should arouse suspicion of a perforated viscus.
- Ultrasound abdomen to rule out other causes of peritonitis such as hollow viscus perforation.

Treatment

- Broad-spectrum antibiotics, such as cefotaxime 2 g IV every eight hours for 5 to 10 days. Intravenous or oral quinolone is an alternative.

- Recurrence of SBP is common and may be reduced by prophylactic quinolones such as norfloxacin (400 mg daily) or ciprofloxacin (250 mg daily).

Q. Discuss the etiology, pathogenesis, clinical features, investigations and management of acute cholangitis.

Q. Charcot's triad.

- Acute cholangitis refers to infection of the bile duct which is characterized by fever, jaundice, and abdominal pain.
- Cholangitis was first described by Charcot.

Etiology

Escherichia coli is the most common organism causing cholangitis.

Pathogenesis

- Acute cholangitis is caused mainly by bacteria.
- The organisms ascend from the duodenum. Hematogenous spread from the portal vein is a rare source of infection.
- The most important predisposing factor for acute cholangitis is biliary obstruction and stasis secondary to biliary calculi or stricture.
- High intrabiliary pressure due to obstruction of biliary tree promotes the migration of bacteria from the portal circulation into the biliary tract and subsequent colonization.
- The sphincter of Oddi normally prevents duodenal reflux into the biliary tree and ascending bacterial infection. When there is sphincter of Oddi dysfunction or after endoscopic sphincterotomy, choledochal surgery, or biliary stent insertion, pathogenic bacteria enter the biliary tree and lead to infection.

Clinical Features

- *Charcot triad*: Refers to fever, right upper quadrant pain, and jaundice. It occurs in only 50 to 75% of patients with acute cholangitis.
- Confusion and hypotension can occur in severe cholangitis.
- Septic shock in severe cases can lead to multiorgan failure.

Investigations

- Leukocytosis with neutrophilia.
- LFT shows cholestatic pattern with elevation of alkaline phosphatase, and predominantly direct hyperbilirubinemia.
- Serum amylase may be elevated due to associated pancreatitis.
- Blood cultures can sometimes identify the organism.
- Ultrasound abdomen may show common bile duct dilatation and stones.
- Endoscopic retrograde cholangiopancreatography (ERCP).
- Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive alternative to ERCP to evaluate biliary tree.
- Endoscopic ultrasound is another means to visualize common duct stones.

Treatment

The mainstays of therapy are antibiotics and establishment of biliary drainage.

General Measures

Intravenous fluids, antipyretics, correction of coagulopathy, and frequent monitoring of vital signs for evidence of sepsis.

Antibiotics

Broad-spectrum antibiotics to cover gram-negative bacteria and enterococcus. Effective antibiotics include: Ampicillin plus gentamicin, carbapenems (imipenem or meropenem) and fluoroquinolones (levofloxacin). Metronidazole can be added to cover anaerobes, in sick patients. Antibiotics should be given for 1 to 2 weeks.

Biliary Drainage

If there is no response to antibiotic therapy, biliary drainage should be considered. Biliary drainage can be achieved by ERCP, a direct percutaneous approach, or open surgical decompression. Endoscopic sphincterotomy with stone extraction and/or stent insertion is now the treatment of choice for establishing biliary drainage in acute cholangitis.

Q. Discuss the etiology, pathology, clinical features, investigations, and management of Budd-Chiari syndrome.

- Budd-Chiari syndrome refers to obstruction of hepatic venous outflow. Obstruction can be anywhere from the small hepatic veins inside the liver to the inferior vena cava and right atrium.
- Most common cause is thrombosis of the hepatic veins and/or the intrahepatic or suprahepatic inferior vena cava.
- Regardless of the cause, patients with Budd-Chiari syndrome develop postsinusoidal portal hypertension, which leads to complications similar to those observed in patients with cirrhosis.

Etiology

- Myeloproliferative diseases
- Malignancy (hepatocellular carcinoma is most common)
- Infections of the liver (amebiasis, hydatid cyst)
- Oral contraceptives
- Pregnancy
- Membranous webs of the inferior vena cava and/or the hepatic veins
- Hypercoagulable states
  - Factor V Leiden mutation
  - Prothrombin gene mutation
  - Antiphospholipid antibody syndrome
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Paroxysmal nocturnal hemoglobinuria
- Behçet's disease
- Idiopathic

Pathology

Initially hepatic congestion affecting the centrilobular areas occurs. This is followed by centrilobular fibrosis and eventually cirrhosis.

Clinical Manifestations

- Budd-Chiari syndrome is more common in women, and usually presents in the third or fourth decade.
- Presentation can be categorized as acute or chronic.
- In acute form, patients usually present with severe right upper quadrant pain, tender hepatomegaly, jaundice and ascites. Fulminant hepatic failure can also occur.
- More gradual occlusion causes gross ascites and often upper abdominal discomfort.
- Peripheral edema occurs when there is inferior vena cava obstruction.
- Cirrhosis and portal hypertension develop in chronic form.

Investigations

- *LFT*: In acute Budd-Chiari, LFT shows acute hepatitis pattern with AST and ALT elevation.
- *Ascitic fluid analysis*: Usually shows exudative pattern.
- *Doppler ultrasound*: Show occlusion of the hepatic veins and reversed flow or associated thrombosis in the portal vein.
- CT scan and MRI may also demonstrate occlusion of the hepatic veins and inferior vena cava.
- *Liver biopsy* shows centrilobular congestion with fibrosis depending upon the duration of the illness.
- *Venography*: This is the gold standard for diagnosis. However, since it is invasive, it is done if CT and MRI are unable to show hepatic venous occlusion.

Treatment

- Treat the underlying cause.
- Medical management involves thrombolysis if thrombosis is of recent origin, and anticoagulation. For anticoagulation, heparin is given initially followed by oral anticoagulation. Ascites is treated with diuretics.
- TIPS followed by anticoagulation: This creates an alternative venous outflow tract. It can be used in extensive hepatic vein occlusion.
- For caval webs or hepatic venous stenosis, decompression via percutaneous transluminal balloon angioplasty with intraluminal stents can maintain hepatic outflow.
- Surgical shunts, such as portacaval shunts, are less commonly performed now that TIPS is available.
- Liver transplantation and lifelong anticoagulation should be considered for progressive liver failure.

Q. Enumerate the tumors of liver.

Q. Discuss the etiology, pathology, clinical features, investigations, and management of hepatocellular carcinoma (hepatoma).

Tumors of Liver

Benign
- Hemangioma
- Hepatic adenoma
- Focal nodular hyperplasia

Malignant
- Primary (hepatocellular carcinoma, fibrolamellar hepatocellular carcinoma, sarcomas)
- Secondaries

Hepatocellular Carcinoma

This is the most common primary liver tumor.

Risk Factors

- Chronic hepatitis B and C infection
- Cirrhosis due to any etiology
- Environmental toxins (aflatoxin)
- Hemochromatosis
- Tobacco and alcohol abuse
- Nonalcoholic steatohepatitis (NASH)

Pathology

- Macroscopically, the tumor appears as a single mass or multiple nodules. Blood supply is from hepatic artery and it tends to spread by invasion into the portal vein and its radicles. Lymph node metastases are common but lung and bone metastases are rare.

- Microscopically, tumor cells resemble hepatocytes when well differentiated.

Clinical Features

- Many patients are asymptomatic and detected through screening programmes.
- Weight loss, anorexia and abdominal pain.
- Variceal hmorrhage can occur due to underlying cirrhosis.
- Examination may reveal ascites, jaundice, hepatomegaly or a right hypochondrial mass. A bruit may be heard over the tumor due to increased blood supply.

Screening

Screening for hepatocellular carcinoma, by ultrasound scanning at 3–6-month intervals, is useful in high-risk patients. This may identify tumor at early stage which may be curable by surgical resection, local ablative therapy or transplantation.

Investigations

Blood tests

- Alpha-fetoprotein (AFP) level is increased in hepatocellular carcinoma. However, it may also increase in active hepatitis due to hepatitis B and C, and in acute hepatic necrosis (e.g. due to paracetamol toxicity).
- ALP is usually elevated but other LFTs may be normal.

Ultrasound

This will detect lesions as small as 2–3 cm. It may also show other underlying pathologies like cirrhosis.

CT

On CT, hepatocellular carcinoma appears hypervascular. It can define the extent and spread of tumors to other organs.

Liver biopsy

- This can confirm the diagnosis of hepatocellular carcinoma and exclude metastatic tumor. There is a small risk of seedling of tumor cells along the needle tract.

Management

Surgical therapy

- *Hepatic resection*: Small localized tumours can be removed by resection in patients with good liver function. Patients with cirrhosis are not suitable for resection because of high-risk of liver failure. However, it can be considered in some cirrhotic patients with small tumors and good liver function.
- *Liver transplantation*: This can be considered in patients with underlying cirrhosis or decompensated liver disease.

Local ablative therapies

- Transcatheter arterial chemoembolization (TACE) is the most commonly offered therapy. TACE is performed by selectively cannulating the feeding artery to the tumor and delivering high local doses of chemotherapy, including doxorubicin, cisplatin, or mitomycin C.
- Another newly developed local treatment is TheraSphere which delivers low-dose brachytherapy to the tumor. TheraSphere uses 20–40 micrometer glass beads that are loaded with radioactive yttrium and delivered angiographically.
- *Radiofrequency ablation*: Under ultrasound guidance, a conducting needle is placed within the tumor and electric current is given. The electric current leads to agitation of the ions in the tissue, heat generation, and desiccation of the tissues surrounding the probe.
- Percutaneous ethanol injection is used rarely and has been replaced by radiofrequency ablation.

Sorafenib

This is a new drug shown to be useful in hepatocellular carcinoma.

Prevention

Hepatitis B vaccination can prevent cancer due to hepatitis B infection.

Q. Alpha-fetoprotein.

- Alpha-fetoprotein (AFP) is a protein produced by the liver and yolk sac of a developing baby during pregnancy. AFP levels go down soon after birth.
- The normal values in males or nonpregnant females is generally less than 40 µg/L.
- AFP levels can increase in the following conditions:
  - Hepatocellular carcinoma
  - Cancer in testes, ovaries, biliary (liver secretion) tract, stomach, or pancreas
  - Cirrhosis of liver
  - Malignant teratoma
- AFP can also be used to monitor tumour reccurence after treatment. Elevation of AFP after remission suggests tumor recurrence. Failure of the AFP value to return to normal by approximately 1 month after surgery suggests the presence of residual tumor.

Q. Discuss the etiology, clinical features, investigations, and management of pyogenic liver abscess.

Pyogenic liver abscess is a type of liver abscess caused by bacteria. Pyogenic liver abscess is curable but fatal if untreated.

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Etiology

- Biliary obstruction causing ascending cholangitis and abscess formation (most common cause)
- Infection via portal system (appendicitis, pylephlebitis)
- Hematogenous via hepatic artery (infective endocarditis, urosepsis)
- Direct extension from adjacent sites
- Trauma (penetrating or non-penetrating injuries)
- Infection of liver tumour or cyst
- Cryptogenic (unknown cause)

Pathogenesis

- Liver abscesses are common in older and immunosuppressed patients.
- Infection can reach the liver in several ways. Commonest route is ascending infection due to biliary obstruction (cholangitis) or direct spread from an empyema of the gallbladder.
- Single abscess is common in the right lobe. Multiple abscesses are usually due to infection secondary to biliary obstruction.
- Common organisms are *E. coli*, streptococci, and bacteroides. Multiple organisms are present in one-third of patients.

Clinical Features

- Patients appear ill with fever, chills and rigors. There may be weight loss. Liver abscess can present as PUO without any localizing symptoms.
- Abdominal pain is usually present and felt in the right upper quadrant, often radiating to the right shoulder.
- Examination shows tender hepatomegaly. Icterus may be present.

Investigations

- Leukocytosis.
- Bilirubin and alkaline phosphatase are elevated. Serum albumin is often low.
- Blood culture may grow the causative organism.
- Ultrasound or CT abdomen is the most useful investigation and shows 90% or more of symptomatic abscesses.
- Needle aspiration under ultrasound guidance confirms the diagnosis and provides pus for culture.
- Chest X-ray may show a raised right diaphragm and lung collapse or an effusion at the base of the right lung.

Management

- Management involves antibiotic therapy and abscess drainage.
- Pending identification of the organism, empirical antibiotic therapy which covers gram-positive, gram-negative and anaerobes should be started. Combination of third generation cephalosporin such as ceftriaxone (covers gram-positive and gram-negative) and metronidazole (covers anaerobes) can be started. Antibiotics should be given for at least four to six weeks.
- Needle aspiration or drainage through a catheter is required if the abscess is large (>5 cm) or if it does not respond to antibiotics.
- Surgical drainage is required for chronic persistent abscess.

Q. Discuss the etiology, clinical features, investigations, and management of amebic liver abscess.

- Amebic liver abscess is the most common extraintestinal manifestation of amebiasis. Amebae reach the liver by ascending the portal venous system.
- It is more common in men.
- A single abscess is found in the right lobe of the liver in most patients, although multiple abscesses can be present in some.

Etiology

- *Entamoeba histolytica.*

Clinical Features

- Fever and abdominal pain in the right upper quadrant.
- Concurrent diarrhea or past history of dysentery may be present.
- Examination shows hepatomegaly and point tenderness over the liver. Jaundice may be present in some.

Diagnosis

- Leukocytosis.
- Elevated alkaline phosphatase and hepatic transaminases.
- Fecal microscopy may show *Entamoeba histolytica* in some patients.
- Ultrasound abdomen can identify the location, size and number of abscesses.
- CT or MRI are more accurate than ultrasound.
- Serologic testing—ant amebic antibodies will be positive in most patients with amebic liver abscess.
- Aspiration—this is required if there is no response to antibiotic therapy after three to five days, if a cyst appears to be at imminent risk of rupture, or to rule out other diagnoses. Aspiration is done under ultrasound or CT guidance. Amebic liver abscess has "anchovy sauce" appearance. Trophozoites may be seen on microscopy of the aspirate.

Treatment

- Both tissue and luminal agents are used in the treatment of amebic liver abscess.
- The most commonly used tissue agent is metronidazole (500 to 750 mg orally three times daily for minimum 10 days). Intravenous therapy is not required as it is well absorbed orally. Other alternatives are tinidazole, ornidazole and nitazoxanide. Chloroquine also has amebicidal activity but is rarely used.
- Luminal agents are used to kill intraluminal organisms. These are paromomycin or diloxanide furoate.
- Aspiration may be required if there is no response to medical therapy.

Q. Liver transplantation.

- Liver transplantation is the treatment of choice for patients with end-stage liver disease.
- The outcome following liver transplantation has improved significantly over the last decade. However, the number of liver transplants is limited by the availability of donors.

Indications

- Fulminant hepatic failure
- Metabolic diseases (hemochromatosis, galactosemia)
- Decompensated cirrhosis
- Hepatocellular carcinoma
- Hepatic trauma

Procedure

- Liver is obtained either from cadavers or from living donors. Full liver can be transplanted from cadavers. Only a portion of the liver is taken from living donors.
- Patients should be maintained on immunospression after transplantation. Less immunosuppression is needed for liver transplantation than for kidney and heart/lung transplantation. Steroids along with tacrolimus or cyclosporin are used for immunosuppression.

Contraindications for Liver Transplantation

- Sepsis
- Extrahepatic malignancy
- Active alcohol or other substance abuse
- Advanced cardiopulmonary disease.

Complications

Early Complications

- Acute rejection
- Surgical complications (hepatic artery thrombosis, anastomotic biliary strictures).
- Infections (pneumonia, wound infections, CMV hepatitis).

Late Complications

- Recurrence of original disease in the graft.
- Complications due to the immunosuppressive therapy such as infections and renal impairment from cyclosporin.
- Chronic vascular rejection.

Q. Enumerate the causes of hemochromatosis.

Q. Discuss the etiology, pathology, clinical features, investigations, and management of hereditary (primary) hemochromatosis.

- Hemochromatosis is a condition where the total body iron is increased and deposited in various organs leading to organ damage including liver.
- It may be hereditary (primary) or secondary.

Causes of Hemochromatosis (Iron Overload States)

Hereditary
- Hereditary hemochromatosis types 1 to 4
- Transferin and ceruloplasmin deficiency

Secondary
- Repeated blood transfusion
- Ineffective erythropoiesis (thalassemia, sideroblastic anemia)
- Liver disease
- Dietary iron overload (prolonged oral iron therapy)
- African iron overload (Bantu siderosis)
- Porphyria cutanea tarda

Pathogenesis

- Hereditary hemochromatosis is caused by mutations in the HFE gene or other related genes which cause increased intestinal iron absorption and iron overload. There are 4 types of hereditary hemochromatosis, types 1 through 4, depending on the gene that is mutated. Type 1 is due to HFE gene mutation. It is inherited as an autosomal recessive disease.
- Transferrin and ceruloplasmin deficiency causes impaired transportation of iron from the organs which gets deposited in various organs.
- Excess iron is deposited throughout the body and total body iron may reach 20–60 gm (normal 4 gm). Important organs involved are liver, pancreatic islets, endocrine glands and heart.
- Excess iron is hazardous, because it produces free radical formation. Free radicals can produce DNA cleavage, impaired protein synthesis, and impairment of cell integrity and cell proliferation, leading to cell injury and fibrosis.

Clinical Features

- Males are affected more commonly (90% of patients are male) as iron loss in menstruation and pregnancy protects females.
- Symptomatic disease usually presents in men aged 40 years or over.
- Many organ systems are involved producing their own clinical manifestations.
- Liver involvement: Cirrhosis, hepatocellular Ca.
- *Heart*: Cardiomyopathy, heart failure, conduction defects.
- *Pancreatic islets*: Diabetes mellitus.
- *Joints*: Arthropathy.
- *Skin*: Leaden-grey pigmentation
- *Testicles*: Atrophy and impotence
- Skin pigmentation along with diabetes is called 'bronzed diabetes'.
- Hemochromatosis patients are prone to develop hepatocellular Ca and other malignancies.

Investigations

- Serum ferritin and iron are increased. TIBC is low.
- CT may show features suggesting excess hepatic iron.
- *Liver biopsy*: Can confirm the diagnosis. It shows heavy iron deposition and hepatic fibrosis. Iron content of the liver can be measured directly.
- *Genetic testing*: Mutations involving the HFE gene can be identified. If HFE gene mutation is absent, mutations of other genes should be suspected.

Management

- *Venesection (phlebotomy)* is the main treatment for hereditary hemochromatosis. It can also be used for secondary hemocromatosis. It is the simplest, cheapest, and most effective way to remove accumulated iron. Weekly venesection of 500 ml blood (250 mg iron) is done until the serum iron is normal; this may take 2 years or more. Thereafter, maintenance venesection is continued as required to keep the serum ferritin normal.
- Chelation therapy is mainly used for secondary hemocromatosis. Deferoxamine is the drug traditionally used for iron chelation therapy and has to be given subcutaneously. Deferasirox and deferiprone are new agents which can be given orally.
- Diabetes and cirrhosis are treated as per standard guidelines.
- First-degree family members should be screened for hemochromatosis by genetic testing and serum ferritin levels.

Prognosis

- Hemochromatosis patients without cirrhosis have a normal life expectancy. Cirrhosis due to hemochromatosis has better prognosis than other forms of cirrhosis. Development of hepatocellular carcinoma in cirrhotic patients is the main cause of death.

Q. Discuss the etiology, pathology, clinical features, investigations, and management of Wilson disease (hepatolenticular degeneration).

- Wilson disease is a rare autosomal recessive disorder of copper metabolism. Here, total body copper is increased, and excess copper is deposited in various organs causing damage.

Etiology and Pathology

- It is caused by a variety of mutations in the gene ATP7B on chromosome 13. ATP7B is a P-type ATPase that is responsible for transport of copper across cellular membranes using ATP as an energy source.
- Normally dietary copper is absorbed from the stomach and proximal small intestine, taken up by the liver, incorporated into ceruloplasmin, and secreted into the blood. Any excess copper is excreted into the bile.
- In Wilson disease, there is failure of synthesis of ceruloplasmin. An impairment in biliary excretion leads to the accumulation of copper in the liver. Over time the liver is progressively damaged and eventually becomes cirrhotic.

Clinical Features

- Most patients present below the age of 40 years.
- Various organs can get damaged due to excess copper accumulation. Most important organs involved are liver and nervous system.
- Liver disease usually occurs in younger age group. It can manifest in many ways such as acute hepatitis, fulminant liver failure, chronic hepatitis and cirrhosis. Wilson disease should be suspected in any case of recurrent acute or chronic liver disease of unknown cause in a patient under 40 years.
- Neurological damage causes basal ganglion syndromes and dementia. Clinical features include a variety of extrapyramidal features, particularly tremor, choreoathetosis, dystonia, parkinsonism and dementia.
- Kayser-Fleischer rings are greenish-brown discoloration of the corneal margin usually first seen at the upper margin due to copper deposition. They are best seen by slit lamp examination and disappear with treatment.
- Other manifestations include renal tubular damage and osteoporosis.

Investigations

- Low serum ceruloplasmin and high serum copper level. However, advanced liver failure from any cause can reduce the serum ceruloplasmin, and occasionally it is normal in Wilson disease.
- 24 hour urinary copper excretion: >40 µg/day is highly suggestive of Wilson disease.
- AST and ALT are usually elevated.
- *Liver biopsy*: Copper content is high. There may be fatty infiltration and portal fibrosis.
- *Genetic testing*: This is limited by the presence of multiple mutations.

Management

- Lifelong therapy is required in patients with Wilson disease and treatment should be given in two phases: Removing the tissue copper that has accumulated and then preventing reaccumulation.
- Copper removal is achieved by the administration of potent chelators. The copper-binding agent penicillamine is the drug of choice. The dose given must be sufficient to produce cupriuresis and most patients require 1.5 g/day. Side effects of penicillamine include rashes, protein-losing nephropathy, lupus-like syndrome and bone marrow suppression. If these side effects occur, trientine dihydrochloride and zinc can be used as alternative agents. Oral zinc acts by preventing copper absorption.
- Prevention of reaccumulation during the maintenance phase can be achieved with lower dose of penicillamine or trientine or zinc. Treatment should not be stopped suddenly as it may precipitate liver failure and it should continue even through pregnancy.
- Patients should be adviced to avoid copper-rich foods such as liver, kidney, shellfish, nuts, beans, peas, chocolate, and mushrooms.
- First degree relatives should be screened for Wilson disease and treatment should be given to affected individuals, even if they are asymptomatic.
- Liver transplantation is indicated for fulminant hepatic failure and decompensated liver disease that are unresponsive to drug therapy.

Prognosis

- The prognosis is excellent, if treatment is started before there is irreversible damage.

Q. Discuss the etiology, pathology, clinical features, investigations, complications and management of acute cholecystitis.

Etiology

- Acute cholecystitis is usually due to obstruction of the gallbladder neck or cystic duct by a gallstone. Rarely, obstruction may be due to mucus, parasitic worms or a tumour.
- Acalculous cholecystitis refers to gallbladder inflammation without gallstones and usually occurs in critically ill patients.

Pathology

- Obstruction leads to inflammation of the gallbladder wall. This leads to mucosal damage which releases phospholipase, converting biliary lecithin to lysolecithin, which is a mucosal toxin. Initially gallbladder contents are sterile, but eventually secondary bacterial infection occurs. Infection with gas-forming organisms can cause emphysematous cholecystitis in elderly and diabetes patients.

Clinical Features

- Patients complain of abdominal pain in the right upper quadrant or epigastrium. Pain may radiate to the right shoulder or back. Pain is steady and severe.
- There may be nausea, vomiting, and anorexia.
- There is often a history of fatty food ingestion before the onset of pain.
- Examination shows a febrile, sick looking patient with tachycardia and tachypnea.
- There is right hypochondrial tenderness, and occasionally a gallbladder mass is palpable.
- There may be guarding in the right hypochondrial area.
- *Murphy's sign*: While palpating gallbladder just below the liver edge, patient is asked to take deep inspiration, causing the gallbladder to descend toward the examining fingers. Patients with acute cholecystitis experience increased pain and may have an inspiratory arrest.

Investigations

- Leukocytosis
- AST, ALT and amylase may be mildly elevated
- *Plain X-rays of the abdomen and chest*: May show radiopaque gallstones, and rarely gas in the gallbladder due to emphysematous cholecystitis or gallbladder perforation. Chest X-ray is also useful to rule out right lower lobe pneumonia which can produce reffered pain in the right hypochondrium and mimick acute cholecystitis.
- *Ultrasound abdomen*: This is the most useful investigation and detects gallstones and gallbladder thickening due to cholecystitis.

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- Cholescintigraphy (also known as HIDA scan—hepatic iminodiacetic acid scan) is indicated if the diagnosis is not sure even after ultrasonography. It involves IV injection of technetium labeled HIDA, which is selectively taken up by hepatocytes and excreted into bile. If the cystic duct is patent, this agent will enter the gallbladder, leading to its visualization. The test is positive if the gallbladder does not visualize, which is invariably due to cystic duct obstruction, usually from edema associated with acute cholecystitis or an obstructing stone.
- *CT scan abdomen*: It can easily demonstrate gallbladder wall edema associated with acute cholecystitis. CT is useful when complications of acute cholecystitis (such as emphysematous cholecystitis or gallbladder perforation) are suspected or when other diagnoses are considered.

Complications

- Gangrene
- Perforation
- Cholecystoenteric fistula
- Gallstone ileus
- Emphysematous cholecystitis.

Management

Medical

- Bed rest, analgesics, intravenous hydration.
- Keep the patient NPO (nil per oral). Nasogastric aspiration through a Ryle's tube is needed if there is persistent vomiting.
- *Antibiotics*: A cephalosporin (such as cefuroxime) plus metronidazole are given intravenously.

Surgical

- Surgery is required if cholecystitis progresses in spite of medical therapy and when complications such as empyema or perforation develop.
- Low risk patients can undergo cholecystectomy. For high risk patients, gallbladder drainage by percutaneous cholecystostomy along with antibiotics is the treatment of choice.

Q. Chronic cholecystitis.

- Chronic cholecystitis refers to chronic inflammation of the gallbladder.
- It is usually due to gallstones.
- Clinical features are recurrent upper abdominal pain, often at night and following a heavy meal. Clinical features are similar to acute calculous cholecystitis but milder.
- Treatment is elective laparoscopic cholecystectomy.

Q. Acute cholangitis.

- Acute cholangitis is caused by bacterial infection of bile ducts. It is usually due to ascending infection from duodenum.
- The most important predisposing factor for acute cholangitis is biliary obstruction and stasis due to biliary calculi; strictures or tumours. It can also occur after ERCP.
- It is characterized by fever, rigors, jaundice, and abdominal pain. Fever, right upper quadrant pain, and jaundice constitute Charcot's triad. Confusion and hypotension can be there in severe cholangitis.
- Investigations show leukocytosis, elevated ALP, and elevated direct bilirubin. Liver enzymes may be mildly elevated. Blood culture may grow the causative organism. Ultrasound abdomen may detect gallbladder or common bile duct stones.
- Treatment is with antibiotics (metronidazole 500 mg IV every eight hours *plus* a third generation cephalosporin, such as ceftriaxone 1 g IV every 24 hours. Underlying cause should be treated.

Q. Gallstone disease (cholelithiasis).

- Gallstone formation in the gallbladder is a common disorder. Gallstones are the commonest cause of gallbladder disease.
- Gallstones are classified into cholesterol stones, pigment stones, and mixed stones. Mixed stones are the commonest.
- Gallstones contain varying quantities of calcium salts, including calcium bilirubinate, carbonate, phosphate and palmitate, which are radiopaque.

Epidemiology

- Gallstones are more common in developed countries. They are less frequent in India, the far East and Africa. It is more common in females.
- Cholesterol stones are most common in developed countries, whereas pigment stones are more frequent in developing countries.

Etiology

- There are many risk factors for development of gallstones

Increased cholesterol secretion
- Female gender
- Pregnancy
- Obesity
- Rapid weight loss

Impaired gallbladder emptying
- Pregnancy
- Gallbladder stasis
- Fasting
- Total parenteral nutrition
- Spinal cord injury

Defective bile salt synthesis
- Old age (impaired bile acid synthesis)
- Cirrhosis of liver (impaired bile acid synthesis)

Excessive intestinal loss of bile salts
- Ileal resection/disease

Miscellaneous
- Hemolysis (increased bilirubin)
- Infected bile

Pathogenesis

- Cholesterol is held in solution in bile by its association with bile acids and phospholipids in the form of micelles and vesicles. Excess cholesterol, or deficiency of bile acids leads to precipitation of cholesterol and cholesterol stone formation. Similarly, excess bilirubin in the bile can precipitate and lead to pigment stone formation.
- 'Biliary sludge' refers to gelatinous bile that contains numerous microspheroliths of calcium bilirubinate granules and cholesterol crystals. It may progress to gallstone formation in many patients.

Clinical Features

- Majority of patients with gallstones are asymptomatic.
- Gall stones can cause epigastric discomfort, fatty food intolerance, dyspepsia and flatulence. Other presentations are biliary colic, acute and chronic cholecystitis.

Complications

- Empyema of the gallbladder
- Porcelain gallbladder (due to precipitation of calcium salts in the gallbladder wall)
- Choledocholithiasis
- Pancreatitis
- Fistulae between the gallbladder and duodenum or colon
- Gallstone ileus
- Cancer of the gallbladder.

Investigations

- Plain X-ray abdomen will show radiopaque gallstones.
- Ultrasonography can demonstrate both radiopaque and radioluscent gallstones and also other abnormalities.
- Oral cholecystography and CT can also be used.
- MRCP can demonstrate gallstones and their complications.

Management

- Asymptomatic gallstones usually do not require treatment.
- Symptomatic gallstones are best treated by open or laparoscopic cholecystectomy.
- Gallstones can be fragmented in the gallbladder (by lithotripsy) or removed mechanically from the common bile duct (by endoscopic sphincterotomy).
- Medical dissolution of gallstones can be achieved by oral administration of the bile acids chenodeoxycholic or ursodeoxycholic acid. Radiolucent gallstones and stones smaller than 15 mm are suitable for medical therapy.

Diseases of Kidney and Urinary Tract

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Q. Describe the structure of a nephron. What are the functions of kidneys?

- Nephron is the functional unit of kidney. Each kidney contains ~1 million nephrons.
- Each nephron consists of the glomerulus, proximal convoluted tubule, loop of Henle and distal convoluted tubule. Filtration of blood occurs at the glomerulus. The collecting ducts of multiple nephrons drain into the renal pelvis and ureter.
- Intralobular branches of the renal artery give rise to the glomerular afferent arterioles which supply the capillaries within the glomerulus. The efferent arteriole supplies the distal nephron.

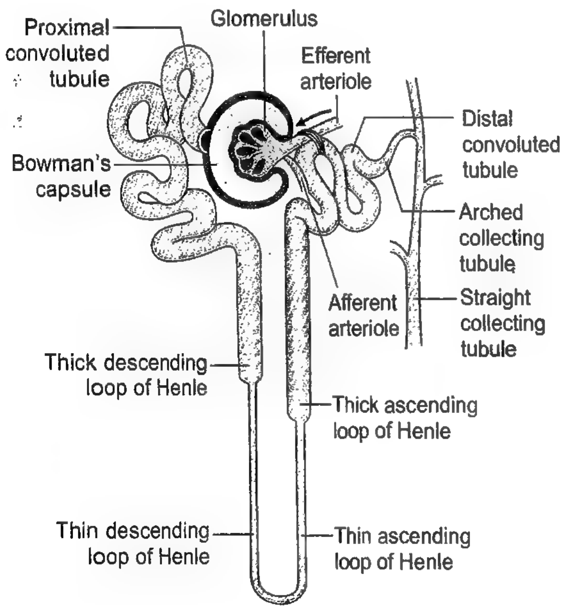

Fig. 8.1: Structure of a nephron

Functions of the Kidneys

Homeostasis

- Maintenance of volume and composition of body fluids.
- Maintenance of acid–base balance.

Excretory Function

- Excretion of metabolic end products (including ammonia, urea and creatinine from protein, and uric acid from nucleic acids), drugs and toxins.

Endocrine Functions

- Production of erythropoietin, which is important for RBC production.
- *Vitamin D metabolism*: It hydroxylates 25-hydroxy-cholecalciferol to 1-25-dihydroxycholecalciferol which is the active form of vitamin D.
- Secretion of renin from the juxtaglomerular apparatus in response to hypotension and changes in sodium content of fluid in the distal convoluted tubule.
- Erythropoietin is produced by the medullary interstitial cells in response to hypoxia. Erythropoietin stimulates erythropoiesis in the bone marrow.

Q. What are the signs and symptoms of kidney and urinary tract disease? How do you approach a suspected case of kidney disease?

- Signs and symptoms of kidney disease may be specific or nonspecific. In the initial stages of kidney disease, patients may be asymptomatic.

History

- Fever occurs in urinary tract infection and pyelonephritis.
- Anuria—total absence or <50 ml urine output per day. Suggests renal failure or urinary outflow obstruction.
- Oliguria refers to urine output of less than 500 ml per day. It also suggests renal failure or urinary outflow obstruction.
- Polyuria is urine output exceeding 3 liters per day. It suggests recovering renal failure or some metabolic cause such as hyperglycemia, hypercalcemia, hypokalemia, etc.
- Loin pain suggests pyelonephritis or renal calculi.
- Severe colicky pain radiating from loin to groin suggests ureteric colic due to ureteric calculi.

- Lower limb swelling associated with early morning facial puffiness suggests renal failure or nephrotic syndrome.
- Dysuria, increased frequency, urgency suggest urinary tract infection. Suprapubic pain is seen in cystitis.
- Impaired urinary flow, hesitancy, dribbling of urine, incomplete emptying of bladder suggest bladder outflow obstruction. Urinary retention, incontinence/enuresis suggest sphincter or bladder wall dysfunction.
- Passing red-colored urine indicates hematuria which can be seen in glomerulonephritis, ureteric stone, Henoch-Schönlein purpura, renal cell carcinoma, etc.
- Passing turbid and frothy urine suggests proteinuria.
- Passing yellow-colored and foul smelling urine suggests urinary tract infection.

Vital Signs

- **Blood pressure:** Hypertension is seen in acute or chronic kidney disease.

General Examination

- Pallor may be seen due to anemia which is due to decreased erythropoietin production in chronic kidney disease.
- JVP may be elevated due to fluid overload state in renal failure.
- Pedal edema and facial puffiness may be seen in nephritic syndrome and fluid overload due to oliguric or anuric renal failure.
- Petechiae and bleeding tendency may be seen due to platelet dysfunction due to uremia.

Abdomen

- Loin pain tenderness (suggests pyelonephritis).
- Suprapubic tenderness suggests cystitis.
- Abdomen may be distended due to urinary retention.
- Sometimes uremia can present as acute abdomen.

CVS

- Pericardial rub may be seen in uremic pericarditis.
- Pericardial effusion is seen in fluid overload state due to renal failure.

RS

- Pulmonary edema and pleural effusion may be seen in cases of acute or chronic renal failure causing fluid overload states.

Nervous System

- Uremia can cause peripheral neuropathy.
- Uremic encephalopathy can occur when there is significant rise in blood urea.
- Electrolyte and fluid imbalances which are common in renal disease can affect nervous system function.

Investigations

- *Blood urea and creatinine* are elevated in renal disease.
- *Urine analysis* can show proteinuria (suggests glomerular disease), hematuria (disease anywhere in the urinary tract), pyuria (seen in glomerulonephritis and UTI), RBC casts (seen in glomerulonephritis).
- *Ultrasound abdomen* shows any structural abnormalities of kidneys and urinary tract. Size of the kidneys, masses, cysts, stones, etc. can be detected by ultrasound abdomen. Shrunken kidneys are seen chronic kidney disease.
- *CT abdomen* can show more details of the findings that are found in ultrasound abdomen. Contrast agent should not be given in renal failure because it is nephrotoxic.
- *Serum electrolytes*: Hyponatremia is seen due to fluid overload. Hyperkalemia is common in both acute and chronic renal failure. Hypocalcemia is seen in chronic kidney disease due to reduced synthesis of 1-25-dihydroxycholecalciferol.
- *Other routine tests*: Such as complete blood count, blood sugar, LFT have to be done.
- *Kidney biopsy* is required in many types of primary and secondary glomerulonephritis and also in suspected renal cell carcinoma.

Diagnosis of Renal Disease Using Above Information

- Using the history, clinical examination findings and investigation data, we have to first narrow down the cause of kidney disease into three types: Prerenal, intrinsic renal, and postrenal problems (*see* the following table).

	Examples
Prerenal disease	Hypovolemic shock, cardiac failure, hypotension
Intrinsic renal disease	Glomerulonephritis, interstitial nephritis, nephrotic syndrome, diabetic nephropathy
Postrenal disease	Renal calculi, prostate hyperplasia, bladder outlet obstruction, urethral stricture

Q. Juxtaglomerular apparatus.

- Juxtaglomerular apparatus is located between the afferent arteriole and the returning distal convoluted tubule of the same nephron. It plays a role in maintaining the volume status of the body.
- The distal convoluted tubule of each nephron comes to lie between the afferent and efferent arterioles of its own glomerulus. The epithelium of distal convoluted tubule

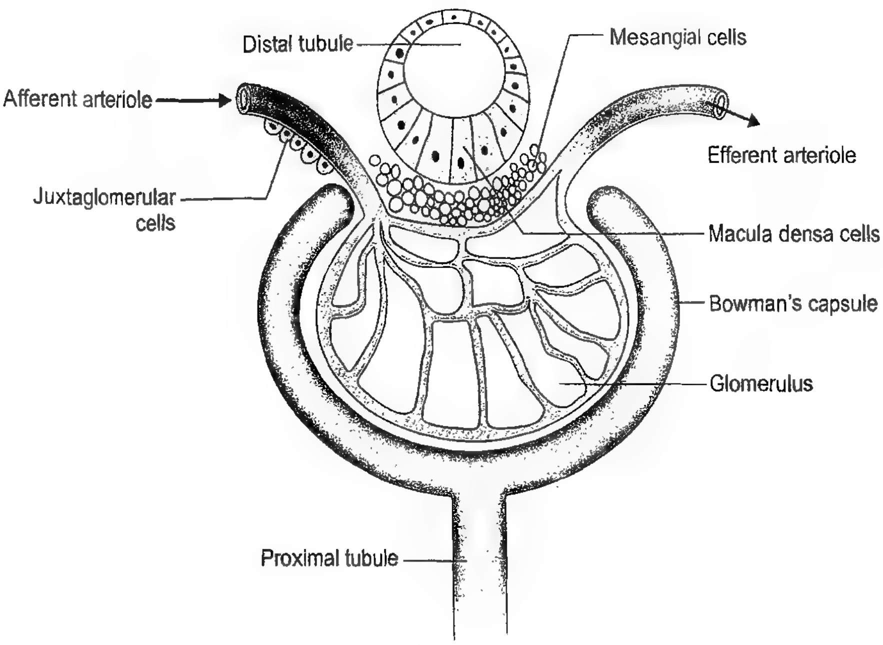

Fig. 8.2: Juxtaglomerular apparatus

is modified in this region, i.e. tubular cells become tall and columnar to form the *macula densa.* The adjacent part of the afferent arteriole is thickened by specialized myoepithelial cells called *juxtaglomerular cells* which have the capacity to secrete renin. The interstitial cells between the distal convoluted tubule and the junction of afferent and efferent arterioles are known as *mesangial* or *lacis* cells. These three components, (1) the macula densa, (2) juxtaglomerular cells and (3) the mesangial cells constitute the juxtaglomerular apparatus.

- Macula densa (of distal tubule) sense the decreased Na Cl delivery to the tubule.
- Mesangial cells regulate the selective vasoconstriction/ vasodilation of the renal afferent and efferent arterioles with mesangial cell contraction.
- Renin is secreted by juxtaglomerular cells wheriever there is reduction in the pressure inside the afferent arteriole or decreased sodium delivery to distal tubule. Renin activates angiotensinogen to angiotensin which undergoes further modification to angiotensin II. Angiotensin II causes constriction of efferent arteriole and systemic vessels thereby increasing glomerular filtration pressure and blood pressure. Angiotensin II also releases aldosterone from the adrenal cortex, which leads to sodium and water retention thereby restoring circulating volume and blood pressure.

Q. Glomerular filtration rate (GFR).

- Glomerular filtration rate (GFR) is the volume of blood filtered through the kidney per minute. It is expressed in ml/min/1.73 m^2. Normal GFR in young, healthy adults is about 120 to 130 ml/min/1.73 m^2 and declines with age.
- GFR is the best overall measure of kidney function. Staging of chronic kidney disease is based on GFR. Dosages of various drugs have to be adjusted based on GFR.
- *Calculation of GFR*: The standard for GFR measurement is inulin clearance. Inulin is neither absorbed nor secreted by the renal tubule and therefore it is the ideal for measuring GFR. However, its measurement is cumbersome and therefore it is mostly used in research settings. There are various creatinine based formulas for estimating GFR which can be used bedside. Commonly used formulas are Cockcroft-Gault formula and the modification of diet in renal disease (MDRD) study equation. The following is Cockcroft-Gault formula.
  Creatinine clearance (ml/min)

$$= \frac{(140 - \text{age}) \times \text{wt (kg)}}{\text{Serum creatinine (mg/dl)} \times 72} \ (\times\ 0.85 \text{ for females})$$

Q. Define the terms "azotemia, anuria, oliguria, polyuria, proteinuria and hematuria".

- *Azotemia*—elevation of urea and ceatinine in the blood. It can be due to prerenal, renal and postrenal causes. All types of azotemia are characterized by decrease in GFR.
- *Anuria*—total absence or <50 ml urine output per day.
- *Oliguria*—urine output of less than 500 ml per day.
- *Polyuria*—urine output exceeding 3 liters per day.

Q. Causes of anuria.

- Bilateral ureteric obstruction
- Prostatic or urethral obstruction
- Bilateral renal arterial occlusion
- Acute tubular necrosis (ATN)
- Shock
- Rapidly progressive glomerulonephritis (RPGN)

Q. Causes of polyuria.

- **Osmotic diuresis:** Hyperglycemia, hypercalcemia, administration of mannitol and radiocontrast agents.
- **Diabetes insipidus:** Central and nephrogenic diabetes insipidus
- **Excessive intake of water:** Psychogenic polydipsia, hypothalamic disease.
- **Renal disorders:** Medullary cystic diseases, resolving ATN or obstruction.
- **Drugs:** Diuretics

Q. Define proteinuria. Enumerate the causes of proteinuria.

- *Proteinuria* is excretion of abnormal amount of protein in the urine. Normal protein excretion is less than 150 mg per day. Out of 150 mg albumin is less than 20 mg. Albumin excretion between 30 and 300 mg per day is called microalbuminuria. Albumin excretion above 300 mg per day is called macroalbuminuria.

Causes of Proteinuria

Glomerular proteinuria
- Glomerular diseases
- Diabetic nephropathy
- Reflux nephropathy and other tubulointerstitial diseases

Overflow proteinuria
- Multiple myeloma

Transient proteinuria
- Fever or heavy exercise

Orthostatic proteinuria
- Increase inprotein excretion in upright position but normal protein excretion when supine

Hemodynamic causes
- Congestive heart failure
- Renovascular hypertension

Q. Define hematuria. Enumerate the causes of hematuria. How do you approach a case of hematuria?

- *Hematuria* is defined as three or more RBCs per high-power field (HPF). Hematuria may be grossly visible (macroscopic hematuria) or detectable only on urine examination (called microscopic hematuria).
- Red urine does not always indicate hematuria. Red urine without hematuria is seen in hemoglobinuria, myoglobinuria, beeturia (due to excess beetroot ingestion), rhubarburia, medications (phenazopyridine, methyl dopa, senna) and porphyria.

Causes of Hematuria

- Glomerular diseases
- Stones
- Cancer of urinary tract (kidney, bladder, prostate)
- Urinary tract infection
- Vigorous exercise
- Sickle cell anemia
- Bleeding disorders
- Trauma
- BPH
- Endometriosis

Approach to a Case of Hematuria

History

- Clues suggesting the site of bleeding.
  - If hematuria is seen at the beginning of micturition and later urine becomes clear, bleeding from urethra is suggested.
  - If hematuria is present throughout micturition uniformly, site of bleeding may be in the bladder or above.
  - Hematuria at the end of micturition (terminal hematuria) suggests bleeding from prostate or bladder base.
- Concurrent pyuria and dysuria suggest urinary tract infection as a cause of hematuria.
- A recent upper respiratory infection suggests post-infectious glomerulonephritis or IgA nephropathy.
- A positive family history of renal disease suggests hereditary nephritis or polycystic kidney disease, or sickle cell disease.
- Unilateral flank pain, which may radiate to the groin, suggests a stone.
- Presence of hesitancy and dribbling in an old man suggests BPH.
- Recent vigorous exercise or trauma may suggest these as the causes of hematuria.
- History of bleeding from multiple sites suggests a bleeding disorder or excessive anticoagulant therapy.

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- Cyclic hematuria in women during menstruation suggests endometriosis of the urinary tract. However, contamination with menstrual blood should be ruled out.

Physical Examination

- *Vitals*: Fever indicates pyelonephritis or UTI. Hypertension indicates glomerulonephritis.
- *General examination*: Pedal edema suggests glomerulonephritis. Presence of rash suggests Henoch-Schönlein purpura, connective tissue disease or SLE.
- *CVS*: Presence of a murmur should raise the suspicion of infective endocarditis especially in the presence of fever.
- *RS*: Presence of crepitations and rhonchi can occur in Goodpasture's syndrome.
- *Abdomen*: Look for any mass (cancer, obstruction) and bruit (renal ischemia). Per rectal examination is done to look for any prostate enlargement.

Lab Tests

- *Urine microscopy* shows presene of RBCs. The presence of red cell casts suggests bleeding from the kidney most often due to glomerulonephritis. Dysmorphic RBCs (with irregular outer cell membrane) and acanthocytes (RBCs with membrane protrusions representing early form of dysmorphic RBCs) suggest hematuria of glomerular origin. Uniform RBCs or presence of clots suggests bleeding from lower urinary tract.
- *Urine cytology* is done if cancer of urinary tract is suspected.
- *Cystoscopy* is subsequently done if malignant and/or atypical/suspicious cells are identified.
- *Imaging* these include plain radiograph of KUB region, intravenous pyelography (IVP), retrograde pyelography, ultrasonography, MRI, and CT scan.
- *Renal biopsy* is required in hematuria of glomerular origin along with the presence of proteinuria and renal failure.
- *Other tests* that are done, are renal function tests, urine for AFB, platelet count, coagulation studies and autoantibodies (ANA, ANCA).

Q. Tamm-Horsfall protein.

- Tamm-Horsfall protein or uromodulin is secreted by thick ascending limb of loop of Henle. It coats the luminal surface of the cell membrane.

Significance of Tamm-Horsfall Protein

- Tamm-Horsfall protein protects against urinary tract infection by binding to fimbriated *Escherichia coli*, which is the main cause of urinary tract infection.
- Tamm-Horsfall protein forms the matrix of all urinary casts. The casts may contain only the matrix (hyaline casts) or can include degenerated cells or filtered proteins (granular casts), or intact cells that are present in the tubular fluid (red, white, or epithelial cell casts).
- Tamm-Horsfall protein may coaggregate with light chains in multiple myeloma and cause cast nephropathy, in which dense intratubular casts occlude the flow of urine and cause renal failure.
- Mutations in the gene encoding for Tamm-Horsfall protein cause familial juvenile hyperuricemic nephropathy and medullary cystic kidney disease. These two disorders are characterized by hyperuricemia, medullary cysts, interstitial nephritis, and progressive renal failure.

Q. Discuss the role of ultrasound in the diagnosis of renal diseases.

- Ultrasound is often the first and only method required for renal imaging.
- It can show renal size and position.
- It can identify obstruction in the urinary tract by detecting dilatation of the collecting system.
- It can identify the location and size of renal calculi.
- It can distinguish tumor, abscess and cyst.
- It can show other abdominal, pelvic and retroperitoneal pathology.
- It can image the prostate and bladder, and estimate completeness of emptying in suspected bladder outflow obstruction.
- In chronic renal disease ultrasonographic density of the renal cortex is increased and corticomedullary differentiation is lost.
- Renal biopsy and cyst puncture can be done under ultrasound guidance.
- Doppler ultrasound is used to show blood flow in extrarenal and intrarenal blood vessels.

Q. Discuss the indications, contraindications and complications of renal biopsy.

- Renal biopsy is used to establish exact diagnosis and also to judge the prognosis and need for treatment.
- It is done percutaneously under ultrasound guidance.

Indications

- Unexplained acute renal failure.
- Chronic renal failure with normal-sized kidneys.
- Nephrotic syndrome or glomerular proteinuria in adults.
- Nephrotic syndrome in children that has atypical features or is not responding to treatment.
- Isolated glomerular hematuria or proteinuria.

Contraindications

- Coagulation abnormalities or thrombocytopenia.
- Uncontrolled hypertension.
- Small hyperechoic kidneys (indicate chronic irreversible disease).
- Solitary kidney (relative contraindication).
- Hydronephrosis.
- Active renal or perirenal infection.
- Skin infection over the biopsy site.
- Uncooperative patient.

Complications

- Pain at biopsy site.
- Hematuria, usually minor but may produce clot colic and obstruction.
- Bleeding around the kidney, occasionally massive and requiring angiography with intervention, or surgery.
- Arteriovenous fistula.
- Rarely, puncture of the liver, pancreas, or spleen may occur.

Q. Define acute kidney injury (acute renal failure). Discuss the causes, clinical features, investigations and management of acute kidney injury.

Definition

- Acute kidney injury (AKI) earlier known as acute renal failure refers to rapid decrease in renal function over days to weeks, causing an accumulation of nitrogenous products in the blood (azotemia).
- It is usually reversible and accompanied by a reduction in urine volume.

Causes

Prerenal
- *Decreased perfusion of kidneys*: Heart failure, septic shock, hepatorenal syndrome, renal artery occlusion/stenosis
- *Volume depletion*: Hemorrhage, vomiting, diarrhea, pancreatitis, burns
- *Drugs*: ACE inhibitors, NSAIDs

Intrarenal
- *Acute tubular necrosis*: Ischemia (causes are the same as for prerenal ARF, but generally the insult is more severe), *infection* (acute pyelonephritis), *toxins* (radiocontrast, aminoglycosides, amphotericin, etc.), hemoglobinuria, myoglobinuria.
- *Glomerular diseases*: Acute glomerulonephritis, RPGN
- *Interstitial nephritis*: Drugs, infections
- *Vascular*: Vasculitis, malignant hypertension

Postrenal
- *Obstruction to urine flow*: Stone, tumor, prostate enlargement, urethral stenosis.

Pathogenesis

- Glomerular filtration occurs due to the pressure gradient from the glomerulus to the Bowman space. Glomerular pressure depends on renal blood flow (RBF) and is controlled by the combined resistances of afferent and efferent arterioles. Almost all the causes of AKI cause reduction in RBF which is the common pathologic pathway for decreasing glomerular filtration rate (GFR). The etiology of AKI consists of 3 main mechanisms: prerenal, renal (intrinsic), and postrenal.
- Prerenal causes are the most common cause of acute renal failure. All prerenal causes act through renal hypoperfusion. If hypoperfusion is rapidly reversed, renal parenchymal damage does not occur. If hypoperfusion persists, ischemia can result, causing intrinsic renal failure.
- Renal causes of AKI either damage glomerulus (glomerulonephritis) or tubules (ATN). Myoglobinuria (derived from rhabdomyolysis) and hemoglobinuria (derived from hemolysis) can cause direct damage to tubular cells. ACE inhibitors prevent efferent renal arteriolar constriction out of proportion to the afferent arteriole leading to decrease in GFR. Nonsteroidal anti-inflammatory drugs (NSAIDs) prevent afferent arteriolar vasodilation by inhibiting prostaglandin-mediated signals.
- Postrenal causes are the least common cause of acute renal failure. It occurs when urinary flow from both kidneys, or a single functioning kidney, is obstructed. This leads to elevated intraluminal pressure in the nephron, causing a decrease in GFR. If the obstruction is relieved, this type of renal failure is reversible.

Clinical Features

- Uremia can cause the following features.
  - Nausea, vomiting, malaise, and altered sensorium.
  - Neurologic examination may show features of encephalopathy with flapping tremors and confusion. Seizures can occur.
  - Platelet dysfunction can lead to bleeding.
- In ATN clinical course can be divided into 3 phases; oliguric phase, maintenance phase and diuretic phase.
- *Oliguric phase*: This is characterized by anuria or oliguria. Signs and symptoms of fluid overload can occur such as pedal edema, ascites, pleural and pericardial effusions. Pericardial friction rub can be present. Pericardial effusions may result in cardiac tamponade. Oliguric phase lasts an average of 10–14 days (can vary from few hours to 4 weeks).
- *Maintenance phase*: This is characterized by low GFR and low urine output continues during this phase. It may last for days to weeks.

- *Diuretic phase*: This is characterized by polyuria and is due to defective urine concentrating ability of tubules. Patient may develop dehydration, hyponatremia and hypokalemia during this phase. After diuretic phase kidney function usually recovers.
- Arrhythmias can occur due to electrolyte imbalance such as hyper- and hypokalemia.
- The lung examination may show crepitations due to volume overload.
- There may be signs and symptoms of underlyng disorder causing renal failure.

Investigations

- Low hemoglobin may be present in prerenal AKI due to hemorrhage. Peripheral blood smear may show schistocytes in conditions such as hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP).
- *Urea and creatinine* are elevated. In prerenal AKI, there is disproportionate elevation of urea in relation to creatinine (usually >20:1).
- *Urine analysis*
  - Urine is acellular and contains transparent hyaline casts in prerenal AKI.
  - RBC and WBC are present in AKI due to glomerulonephritis. RBC casts indicate glomerular injury or rarely interstitial nephritis.
  - WBC casts and nonpigmented granular casts suggest interstitial nephritis, whereas broad granular casts are characteristic of chronic kidney disease and probably reflect interstitial fibrosis and dilatation of tubules.
  - Pigmented "muddy brown" granular casts and casts containing tubule epithelial cells are characteristic of ATN. RBC and WBC may also be present in intraluminal obstruction or prostatic disease, but casts are typically absent.
  - Eosinophiluria (>5% of urine leukocytes) suggests allergic interstitial nephritis.
  - Abundant uric acid crystals suggest acute urate nephropathy.
  - Proteinuria of >1 g/d suggests glomerular damage or excretion of myeloma light chains. Hemoglobinuria or myoglobinuria should raise the possibility of renal failure due to hemolysis and rhabdomyolyis.
- *Electrolyte abnormalities* include hyperkalemia, hypocalcemia and hyperphosphatemia.
- *ECG* may reveal changes of hyperkalemia and also any cardiac problems.
- *Anti-streptolysin O titre*: If post-streptococcal glomerulonephritis is suspected.
- *Other serology*: If clinically suspected, e.g. hepatitis B, hepatitis C, leptospirosis, syphilis, hantavirus.
- If diagnosis is not clear from above investigations consider ANA, ANCA, complement levels, etc. to rule out connective tissue disorder.
- *Emerging biomarkers*: Creatinine elevation is a late marker for renal failure; hence, search is on for other markers which can predict renal failire early. Urinary neutrophil gelatinase-associated lipocalin (NGAL) has been shown to be a strong predictor of early AKI. Another marker is serum cystatin C, which though not as sensitive as creatinine level for detecting AKI, can identify a subset of AKI patients at higher risk for adverse outcomes.
- *Renal ultrasound* is usually required urgently especially renal failure due to obstruction is suspected. *Renal Doppler* can identify patency of renal arteries and veins.
- *Chest X-ray* may show evidence of pulmonary edema.
- *Renal biopsy* is indicated when renal function does not return for a prolonged period and a prognosis is required to develop long-term management.

Management

- Correct the underlying cause of the AKI.
- Treat fluid and electrolyte abnormalities. Loop diuretics such as frusemide or torsemide can be used if there is fluid overload. On the other hand fluids should be given if there is hypovolemia causing renal failure. Hyperkalemia should be corrected by antihyperkalemia measures such as salbutamol nebulization, potassium binding resins, etc.
- Correct metabolic acidosis with oral or IV bicarbonate.
- Nephrotoxic drugs such as NSAIDs, aminoglycosides, etc. should be avoided.
- Restriction of water (unless there is hypovolemia), Na, phosphate, and K intake, but provision of adequate protein.
- Hemodialysis is required for the following if conservative measures fail.

Indications for Hemodialysis

- Urea >180 mg/dl and creatinine >8 mg/dl.
- Refractory fluid overload with pulmonary edema.
- Resistant hyperkalemia.
- Severe metabolic acidosis (pH less than 7.1).
- Signs of uremia, such as pericarditis, neuropathy, or altered mental status.

Q. Define chronic kidney disease (CKD). Discuss the causes, clinical features, investigations, and management of CKD.

- *Chronic kidney disease (CKD)* (earlier known as chronic renal failure) is defined as either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for 3 or more months.
- CKD can be divided into following stages:

Stage 1: Kidney damage with normal or increased GFR (>90 ml/min/1.73 m^2)
Stage 2: Mild reduction in GFR (60–89 ml/min/1.73 m^2)
Stage 3: Moderate reduction in GFR (30–59 ml/min/1.73 m^2)
Stage 4: Severe reduction in GFR (15–29 ml/min/1.73 m^2)
Stage 5: Kidney failure (GFR <15 ml/min/1.73 m^2 or dialysis)

- CKD stages 1 and 2 cannot be diagnosed based on GFR alone as GFR can be normal in these stages. Stage 5 CKD is also known as end-stage renal disease (ESRD).

Etiology of CKD/CRF

Primary glomerular diseases
- Focal and segmental glomerulosclerosis (FSGN)
- Membranoproliferative glomerulonephritis (MPGN)
- IgA nephropathy
- Membranous nephropathy

Secondary glomerular diseases
- Diabetic nephropathy
- Hypertension
- Amyloidosis
- Postinfectious glomerulonephritis
- HIV-associated nephropathy
- Collagen-vascular diseases
- Sickle cell nephropathy

Tubulointerstitial nephritis
- Drugs
- Heavy metals
- Analgesic nephropathy
- Reflux/chronic pyelonephritis
- Idiopathic

Obstructive nephropathies
- Prostate enlargement
- Calculus
- Retroperitoneal fibrosis
- Tumor

Vascular diseases
- Renal artery stenosis
- Vasculitis

Hereditary diseases
- Polycystic kidney disease
- Medullary cystic disease
- Alport's syndrome

Clinical Features

Fluid and Electrolyte Imbalance

- In most patients with stable CKD, there is retention of sodium and water leading to fluid overload. Fluid overload manifests as peripheral edema, ascites, pleural and pericardial effusions. It contributes to development of hypertension also. Rarely hyponatremia is seen (dilutional hyponatremia), and responds to water restriction.
- Hyperkalema is seen in CKD, as potassium excretion is impaired. Rarely hypokalemia is seen as a result of renal potassium wasting in diseases such as Fanconi's syndrome, renal tubular acidosis, or other forms of hereditary or acquired tubulointerstitial disease. However, even in these conditions, as the GFR declines, hyperkalemia becomes common.

Acid–base Disturbance

- Metabolic acidosis is common due to inability to excrete acid load due to less ammonia formation in the kidneys. In severe metabolic acidosis, patient may have deep respiration (Kussmaul's respiration), anorexia, nausea, vomiting, hiccoughs, pruritus, muscular twitching, fits, drowsiness and coma.

Uremia

- Uremia refers to a constellation of signs and symptoms seen in renal failure. Manifestations of the uremic state include anorexia, nausea, vomiting, growth retardation, peripheral neuropathy, and CNS features such as altered sensorium, seizures, and coma.
- Bleeding may occur due to abnormal platelet adhesion and aggregation due to uremia.
- Pericarditis and pericardial effusion also occurs in uremia and is an indication for dialysis.

Disturbances in Calcium and Phosphate Metabolism

- *Renal osteodystrophy*: Kidney is the site of formation of 1-25-dihydroxycholecalciferol (active vit D). Diminished active vit D formation in CKD leads to hypocalcemia and hyperphosphatemia (due to phosphate retention). Hypocalcemia and hyperphosphatemia stimulate PTH production. Increased PTH (hyperparathyroidism) stimulates bone turnover and leads to osteitis fibrosa cystica characterized by marrow fibrosis and bone cysts.

Anemia

- Anemia is due to reduced renal erythropoietin production. It is normocytic and normochromic.

Hypertension

- Hypertension is due to volume expansion and/or activation of the renin-angiotensin system.

Dyslipidemia and Atherosclerosis

- Abnormal lipid metabolism is common in patients with CKD. Typically triglyceride and cholesterol levels are increased and add to the risk for cardiovascular disease.

Endocrine Dysfunction

- CKD has effects on many endocrine systems.
- *Growth hormone*—there is end-organ resistance to GH action due to increased levels of insulin growth factor binding proteins. This contributes to growth impairment especially in children.
- *Thyroid function*—there is low T3 and T4, normal TSH level, and normal or decreased thyroid hormone-binding globulin levels. These findings are consistent with the "Sick euthyroid syndrome" seen in other chronic diseases.
- *Gonadal hormones*—there are abnormalities in gonadal hormones in both male and female patients, which result in delayed puberty in two-thirds of adolescents with ESRD. Males have reduced testosterone levels and elevated LH and FSH. Females have reduced serum estrogen, elevated LH and FSH, and loss of the LH pulsatile pattern. These disturbances result in anovulation.

Growth Impairment

- Growth failure is common in childhood CKD, and is multifactorial. It is due to metabolic acidosis, decreased caloric intake, renal osteodystrophy, and alterations in growth hormone metabolism.

Investigations

- Urea and creatinine are elevated. The level of serum creatinine correlates with the degree of renal impairment.
- *Urine analysis* shows fixed specific gravity of around 1.010 (isosthenuria, because of loss of urine concentrating ability of kidneys) and presence of broadcasts. WBCs are present in the urine in UTI, papillary necrosis, BPH and renal tuberculosis. Eosinophils are present in allergic tubulointerstitial disease. RBC casts are seen in glomerulonephritis.
- *Serum electrolytes*: Hyperkalemia, hypocalcemia, and hyperphosphatemia are seen. Bicarbonate levels are reduced.
- Anemia is seen which is usually normocytic normochromic.
- *Ultrasound abdomen*: Usually shows bilateral small-sized kidneys. Ultrasound can also rule out obstruction, polycystic kidney disease, etc.
- *Chest X-ray* may show pulmonary edema and pericardial effusion.
- *ECG* may show signs of hyperkalemia or cardiac disease.
- *Renal artery Doppler*: If renal artery stenosis is suspected.
- Hepatitis B, C and HIV serology, if dialysis is needed (vaccination against hepatitis B if no previous infection; isolation of dialysis machine if positive).
- ANA if connective tissue disease is suspected.
- ANCA if vasculitis is suspected.
- Renal biopsy to establish the diagnosis in selected cases.

Management

- Management of CKD involves the following issues:
  - Treatment of underlying cause of CKD.
  - Correction of reversible factors contributing to renal failure.
  - Preventing or slowing the progression of CKD.
  - Treatment of complications of renal failure.
  - Renal replacement therapy.

Treatment of Underlying Cause

- Identify the underlying cause of renal failure and institute treatment for that. For example, control of diabetes, hypertension, immunosuppression in glomerulonephritis, etc.

Reversible Factors in Chronic Renal Failure

- Hypertension
- Renal artery stenosis
- Hypotension
- Hypovolemia
- Cardiac failure
- Urinary tract obstruction
- Urinary tract infection
- Infections
- Nephrotoxic drugs

Slowing the Progression of CKD

- ACE inhibitors have been shown to slow the progression of CKD in diabetics. ACE inhibitors should be used, where tolerated. Monitor creatinine and potassium after starting on ACE inhibitors as there can be worsening of GFR and hyperkalemia. Angiotensin II receptor antagonists also have similar effect.
- Restriction of dietary protein intake also delays the progression of CKD.

Treatment of the Complications of Renal Failure

- *Anemia*: Recombinant human erythropoietin is effective in correcting the anemia of CRF. Severe anemia should be corrected by blood transfusion.

- *Volume overload* should be treated by a combination of dietary sodium restriction and diuretic therapy, usually with a loop diuretic given daily.
- *Hyperkalemia*
  - Avoid potassium rich foods such as coconut water, fruit juices, etc.
  - Loop diuretics such as frusemide to increase urinary potassium losses.
  - Potassium binding agents (Kayexalate 5 gm with each meal).
  - Salbutamol nebulizations.
  - 50% dextrose 100 ml with 10 units of insulin infusion 8th hourly. This will push the potassium into the cells and dereases serum potassium.
  - Bicarbonate infusion or orally will also decrease potassium.
- *Metabolic acidosis*: Sodium bicarbonate (in a daily dose of 0.5 to 1 mEq/kg per day) should be given to maintain serum bicarbonate concentration above 22 mEq/L. Sodium citrate may be used in patients unable to tolerate sodium bicarbonate.
- *Hyperphosphatemia*: This is treated by oral phosphate binders to maintain serum phosphorus levels less than 5 mg/dl. Calcium carbonate or calcium acetate can be used as phosphate binders, but have the risk of causing hypercalcemia. The nonabsorbable agent sevelamer is a cationic polymer that binds phosphate through ion exchange. Sevelamer controls the serum phosphate concentration without inducing hypercalcemia.
- *Renal osteodystrophy*: This is treated by calcitriol (1, 25-dihydroxyvitamin D) and control of phosphate levels.
- *Hypertension* is controlled by a combination of antihypertensives and diuretics. ACE inhibitors or angiotensin II receptor blocker can be used initially if creatinine is not high. Other antihypertensives are calcium channel blockers, clonidine, beta bolockers, and alpha blockers.
- *Abnormal lipids*: Hypercholesterolemia is almost universal in patients with significant proteinuria, and increased triglyceride levels are also common in patients with CKD. This can be controlled with HMG-CoA reductase inhibitors (e.g. atorvastatin, rosuvastatin).
- *Bleeding* is due to abnormal platelet function. Dialysis can partially correct the bleeding tendency.

Renal Replacement Therapy

- If conservative measures are inadequate, hemodialysis must be planned.
- Renal transplantation can be considered in suitable patients.

Q. Distinguishing acute kidney injury (AKI) from chronic kidney disease (CKD).

Table 8.1 Distinguishing acute kidney injury (AKI) from chronic kidney disease (CKD)

Finding	Comment
Previously documented elevation of serum creatinine	Most reliable evidence of CKD
Small kidneys on ultrasound	Seen in CKD
Normal or enlarged kidneys on ultrasound	Usually favors AKI. Can be seen in some forms of CKD (diabetic nephropathy, polycystic kidney disease, myeloma, rapidly progressive glomerulonephritis, infiltrative diseases, amyloidosis, obstruction)
Oliguria, daily increases in serum creatinine and BUN	Favors AKI
Eye-band keratopathy	Favors CKD
Presence of anemia	Favors CKD
Hypocalcemia	Favors CKD

Q. Renal osteodystrophy [CKD-mineral and bone disorder (CKD-MBD)].

- The term renal osteodystrophy refers to the pathological changes in bone structure that occur in chronic kidney disease (CKD). However, this term is now being replaced by the new term 'CKD-mineral and bone disorder (CKD-MBD)' because it refers only to bony changes. But the new term CKD-mineral and bone disorder (CKD-MBD) defines the entire mineral, bone, hormonal, and calcific cardiovascular abnormalities that are seen in CKD.
- Renal osteodystrophy consists of a mixture of osteomalacia, osteitis fibrosa cystica (due to secondary hyperparathyroidism), osteoporosis and osteosclerosis.

Pathogenesis

- CKD leads to diminished conversion of cholecalciferol to its active metabolite, 1,25-dihydroxycholecalciferol in the kidneys. Diminished 1,25-dihydroxycholecalciferol leads to diminished intestinal absorption of calcium, hypocalcemia and reduction in the calcification of osteoid in bone leading to osteomalacia.
- Hypocalcemia and hyperphosphatemia stimulate parathyroid glands which lead to secondary hyperparathyroidism.
- Secondary hyperparathyroidism leads to osteitis fibrosa cystica. In some patients tertiary or autonomous hyperparathyroidism with hypercalcemia develops.

- The reason for osteosclerosis is not clear. It is seen mainly in the sacral area, at the base of the skull and in the vertebrae.
- Vascular calcification especially of coronary arteries is another important feature of CKD-MBD which has been ignored earlier. This can lead to acute coronary events contributing to increased mortality in CKD patients.

Clinical Features

- Can be asymptomatic.
- If symptomatic, signs and symptoms include bone pain, joint pain, bone deformation and bone fracture.

Investigations

- Blood tests will show decreased calcium and calcitriol (vitamin D_3) and increased phosphate and parathyroid hormone.
- X-rays will show chondrocalcinosis at the knees and pubic symphysis, osteopenia, osteitis fibrosa cystica and bone fractures.

Management

- Serum calcium and phosphate levels should be kept as near to normal as possible. Hypocalcemia is corrected by giving calcium supplements and active vit D_3. Hyperphosphatemia is controlled by avoiding phosphate rich foods (milk, cheese, eggs) and by giving phosphate-binding drugs with food.
- Parathyroidectomy may be needed in severe bone disease with autonomous parathyroid function.
- Regular hemodialysis improves the prognosis of these patients. Kidney transplantation has been shown to reverse the disease process.

Q. Discuss the etiology, clinical features, investigations and management of nephrotic syndrome.

- Nephrotic syndrome is defined as proteinuria of more than 3 gm/day due to a glomerular disorder accompanied by hypoalbuminemia and edema.

Etiology

Idiopathic or primary nephrotic syndrome
- Minimal change disease
- Focal segmental glomerulosclerosis (FSGS)
- Membranous nephropathy
- Membranoproliferative glomerulonephritis
- Other proliferative and sclerosing glomerulonephritides

Secondary nephrotic syndrome
- Diabetes mellitus
- SLE and other collagen diseases
- Amyloidosis
- Vasculitis (Wegener's granulomatosis, rapidly progressive glomerulonephritis, Goodpasture's syndrome, etc.)
- Infections (post-streptococcal, hepatitis B, hepatitis C, HIV infection, filariasis)
- Drugs (penicillamine, NSAIDs, lithium, street heroin)
- Malignancy (Hodgkin's lymphoma, leukemia)
- Pregnancy-related (includes preeclampsia)
- Unilateral renal artery stenosis
- Massive obesity—sleep apnea
- Reflux nephropathy

Pathophysiology

- Nephrotic syndrome is characterized by proteinuria. hypoalbuminemia and peripheral edema.
- Proteinuria occurs because of damage to glomerular capillary endothelial cells, the glomerular basement membrane (GBM), or podocytes, which normally filter serum protein selectively by size and charge.
- Hypoalbuminemia is due to urinary protein loss. Catabolism of filtered albumin by the proximal tubule as well as redistribution of albumin within the body also contribute to hypoalbuminemia.
- Salt and water retention in nephrotic syndrome can be explained by two different mechanisms. In the classic theory, proteinuria leads to hypoalbuminemia, a low plasma oncotic pressure, and intravascular volume depletion leading to underperfusion of the kidneys. This stimulates renin-angiotensin system causing increased renal sodium and water retention. Decreased oncotic pressure in the capillaries also causes fluid leakage and edema.
- Another mechanism may be primary renal sodium retention at a distal nephron site, perhaps due to altered responsiveness to hormones such as atrial natriuretic factor.

Clinical Features

- Nephrotic syndrome occurs at any age but is more prevalent in children, mostly between ages 1½ and 4 yrs.
- Peripheral edema is the hallmark of the nephrotic syndrome. Initially it is noted in the dependent areas such as the lower extremities, but later becomes generalized. Early morning facial puffiness is seen in most patients even before the development of generalized edema.
- Patients can experience dyspnea due to pulmonary edema and pleural effusion.
- Ascites may be present.
- Patients are more prone to infection due to loss of immunoglobulins and complements in the urine.

- Patients also have hypercoagulable state due to urinary losses of antithrombin III, protein C, protein S, and increased platelet activation. Patients are prone to renal vein thrombosis and other venous thromboemboli.
- Microcytic hypochromic anemia may result from loss of transferrin in the urine.
- Vit D deficiency may result from loss of cholecalciferol binding protein.

Investigations

- Urine analysis shows heavy proteinuria. 24-hour urine protein excretion should be measured and it shows nephrotic range proteinuria (>3 gm/day). Normal protein excretion is <150 mg/day. Minimal hematuria may also be present.
- Serum albumin is low (<3 g/dl).
- Urea and creatinine may be elevated if there is renal failure.
- Total cholesterol and LDL-cholesterol is elevated in most patients. HDL-cholesterol is normal or decreased.
- Blood sugar and glycosylated hemoglobin tests for diabetes.
- Antinuclear antibody (ANA) and ANCA test for collagen vascular disease and vasculitis.
- Serum anticoagulants and complement levels are decreased.
- Hepatitis B and C serology, HIV serology.
- Renal biopsy if the cause is not clear especially in an adult patient.

Management

Protein Loss

- The daily total dietary protein intake should replace the daily urinary protein losses so as to avoid negative nitrogen balance. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers reduce the amount of proteinuria.

Edema

- This can be managed by dietary salt restriction and diuretics. Commonly used diuretics include thiazide and loop diuretics.

Hyperlipidemia

- Dietary modification and exercise should be adviced. HMG-CoA reductase inhibitors (statins) can be used in patients not responding to dietary measures.

Hypercoagulable State

- Anticoagulation therapy is given for at least 3–6 months in patients with evidence of thrombosis. Patients with renal vein thrombosis and recurrent thromboemboli require indefinite anticoagulation.

Treatment of the Underlying Cause

- Minimal change disease responds to steroids.
- Steroids are beneficial in only 20–30% cases of focal segmental glomerulosclerosis (FSGS). Cyclophosphamide and cyclosporin are alternatives.
- Membranous nephropathy responds to alternating monthly corticosteroids and monthly oral chlorambucil over 6 months. Recent controlled studies using only corticosteroids for 6 months have shown similar beneficial results. Membranous nephropathy with progressive renal failure may benefit from cyclophosphamide plus corticosteroids.

Q. Minimal change disease (nil disease or lipoid nephrosis).

- Minimal change disease accounts for most cases of nephrotic syndrome in children and 10 to 15% of idiopathic nephrotic syndrome in adults.
- Most of the cases are idiopathic but some cases are associated with drugs (NSAIDs, lithium) and hematological malignancies (Hodgkin's disease and leukemias).

Clinical Features

- Patients typically present with periorbital and peripheral edema. Periorbital edema is noted first.
- Malaise, easy fatigability and weight gain.
- Hypertension is rare.

Investigations

- Urea and creatinine are normal.
- Urine analysis shows nephrotic range proteinuria and occasionally hematuria. RBC casts are absent.
- Serum albumin is low.
- Serologic work up (including antinuclear antibodies and complements) is normal.
- Kidney biopsy is usually not required in children except in atypical cases. However, kidney biopsy is required in adults. Biopsy shows no glomerular abnormalities on light microscopy. The tubules may show lipid droplet accumulation from absorbed lipoproteins (hence also called lipoid nephrosis). Complement and Ig deposits are absent on immunofluorescence. Electron microscopy shows effacement or "fusion" of the foot processes of epithelial podocytes.

Treatment

- Initial therapy is with steroids, prednisolone 60 mg/m^2 per day (maximum of 60 mg/day). When proteinuria disappears, prednisolone is continued at the same dose for 1 month and then on alternate day (at the same daily

dose) for 2 months. Thereafter, the alternate day dose is gradually decreased.

- Complete remission occurs in >80% of patients treated with corticosteroids, and treatment is usually continued for 1 to 2 years.
- Response may be slower in adults, and they should not be considered steroid-resistant until they have failed to respond to 4 months of treatment.
- Relapses can occur in children and adults. First relapse is treated similarly as the initial episode. Patients who relapse third time or who become steroid dependent may be treated with a 2-month course of an alkylating agent (cyclophosphamide 2 mg/kg/day or chlorambucil). Another alternative is low dose cyclosporin (4 to 6 mg/kg/day for 4 months), but this carries the risk of nephrotoxicity.

Q. Discuss the etiology, clinical features, investigations and management of glomerulonephritis (nephritic syndrome).

- Glomerulonephritis literally means 'inflammation of glomeruli'. Here the glomeruli are damaged due to inflammation. Glomerulonephritis classically presents with hematuria, RBC casts, pyuria (WBCs), mild to moderate proteinuria and hypertension.

Etiology

Primary glomerular diseases
Diffuse proliferative glomerulonephritis, focal segmental glomerulosclerosis (FSGS), membranous glomerulonephritis, membranoproliferative glomerulonephritis, cresentic glomerulonephritis, IgA nephropathy.

Systemic diseases
SLE, Wegener's granulomatosis, polyarteritis, Henoch-Schönlein purpura, Goodpasture's syndrome, sickle cell nephropathy.

Infections
Post-streptococcal glomerulonephritis, syphilis, subacute bacterial endocarditis, hepatitis B and C, HIV infection, infectious mononucleosis, cytomegalovirus, malaria, schistosomiasis.

Miscellaneous
Malignancy, eclampsia, serum sickness, drugs (penicillamine), malignant hypertension.

Pathogenesis

- Most types of glomerulonephritis are immunologically mediated. Glomerular injury occurs by two main mechanisms, either by deposition of antibody in the glomerular basement membrane or by deposition of immune complexes.
- Immune complexes are formed *in situ* by antibodies which complex with glomerular antigens, or with other antigens ('planted' antigens, e.g. viral or bacterial ones) that have localized in glomeruli.
- The antibodies and immune complexes trigger injury by complement activation, fibrin deposition, release of cytokines and recruitment of inflammatory cells.

Clinical Features

- Patient presents with hematuria, hypertension, oliguria and edema. Edema is found first in body parts with low tissue tension, such as the periorbital and scrotal regions.

Investigations

- Urine analysis shows hematuria, moderate proteinuria (usually <2 g/d), RBC casts, and WBCs. Red cell casts are specific for glomerulonephritis.
- Complement levels (C3, C4) are usually decreased.
- ASO titre may be increased in post-streptococcal glomerulonephritis.
- Anti-GBM antibody levels are elevated.
- ANCA, ANA if connective tissue disease is suspected.
- Hepatitis serologies.
- Renal ultrasound.
- Renal biopsy if the cause is not clear.

Treatment

- Depending on the nature and severity of disease, treatment may involve high-dose steroids and cytotoxic agents such as cyclophosphamide.
- Plasmapheresis can be used in Goodpasture's disease as a temporary measure until chemotherapy takes effect.
- Underlying disease requires specific treatment.

Q. What are the differences between nephrotic and nephritic syndrome?

Table 8.2 Differences between nephrotic and nephritic syndrome

	Nephrotic syndrome	Nephritic syndrome
Proteinuria	Massive (>3 gm/day)	Moderate (<2 gm/day)
Hematuria	Minimal	Significant
RBC casts in urine	Absent	Present
Hypoalbuminemia	Present	Rarely
Generalized edema	Present	Rarely present in cases of renal failure
Hyperlipidemia/ hyperlipiduria	Yes	No
Hypertension	Absent	Present
Urea and creatinine	Usually normal	Often elevated

Q. Discuss the etiology, pathogenesis, clinical features, investigations, complications, and management of post-streptococcal glomerulonephritis.

- Post-streptococcal glomerulonephritis is acute glomerulonephritis occurring after infection with streptococci.

Etiology

- Group A beta-hemolytic streptococci are responsible for post-streptococcal glomerulonephritis. Skin and throat infections with this organism are followed by glomerulonephritis.

Pathogenesis

- Post-streptococcal glomerulonephritis is an immune-mediated disease involving streptococcal antigens, circulating immune complexes, and activation of complement in association with cell-mediated injury.
- Many streptococcal antigens have biochemical affinity for glomerular basement membrane and in this location act as target for antibodies.
- The immune response to these antigens leads to acute glomerulonephritis.

Clinical Features

- It occurs in children between the ages of 5 and 15 years, but can occur in adults also.
- It is more common in males.
- Patient presents with hematuria, proteinuria, pyuria, red blood cell casts, edema, hypertension, and oliguric renal failure.
- Systemic symptoms of headache, malaise, anorexia, and flank pain (due to swelling of the renal capsule) may be present.
- Subclinical disease is common and is characterized by asymptomatic microscopic hematuria.

Investigations

- Urine analysis shows hematuria, proteinuria, pyuria, and RBC casts. Proteinuria can sometimes be in the nephrotic range.
- Urea and creatinine may be elevated.
- Serum complement levels are low.
- Streptococcal culture may be positive from the infected site (throat or skin).
- ASO titre, anti-DNAse or antihyaluronidase antibodies are increased.
- Renal biopsy is rarely required. It shows mesangial and endothelial cell proliferation, glomerular infiltration with polymorphonuclear leukocytes, granular subendothelial immune deposits and subepithelial deposits.

Complications

- Pulmonary edema, hypertensive encephalopathy, and permanent renal failure.

Management

- Treatment is mainly supportive.
- The measures are salt restriction, diuretics, antihypertensives and dialysis if required.
- Antibiotic treatment for streptococcal infection should be given to all patients and their cohabitants. Antibiotic choices are pencillins (ampicillin, amoxicillin) or cephalosporins or macrolides or clindamycin. Oral penicillin V and amoxicillin are the 1st drugs of choice and are given for 10 days.
- Steroids and cytotoxic drugs are of no value.
- Prognosis is good and permanent renal failure is uncommon.

Q. IgA nephropathy.

- IgA nephropathy is the most common type of primary glomerulonephritis. It is a common cause of renal failure.
- It is characterized by deposition of IgA immune complexes in glomeruli manifesting as slowly progressive hematuria, proteinuria, and often renal insufficiency. Sometimes it can progress rapidly causing rapidly progressive glomerulonephritis (RPGN).

Pathogenesis

- Exact pathogenesis is unknown, but evidence suggests that there may be several mechanisms, including increased IgA production, defective IgA glycosylation causing increased binding to mesangial cells, decreased IgA clearance, a defective mucosal immune system, and overproduction of cytokines stimulating mesangial cell proliferation.

Clinical Features

- It occurs in all age groups but more common in young adults. Males are more commonly affected.
- Patient presents with gross painless hematuria, proteinuria and hypertension within 1–2 days following a mucosal infection (respiratory tract, GI tract). Hematuria is usually recurrent or persistent. There may be acute exacerbations of hematuria in association with respiratory tract infections.

Diagnosis

- IgA nephropathy should be suspected in patient who presents with gross hematuria, particularly within 2 days of a febrile mucosal illness or with flank pain.

8

- Urinalysis.
- Renal biopsy shows mesangial deposition of IgA and complement (C3) on immunofluorescent staining. IgA deposits are not specific for IgA nephropathy because similar IgA deposits are also seen in other diseases such as Henoch-Schönlein purpura.

Treatment

- Patients with mild disease should be monitored at 6 to 12-month intervals to assess for disease progression. Patients with persistent proteinuria should be treated with an ACE inhibitor. Omega-3 fatty acids found in fish oil have been shown to be beneficial. Patients with progressive disease should be treated by intravenous methylprednisolone 1 gm daily for three consecutive days.

Q. Rapidly progressive glomerulonephritis (crescentic glomerulonephritis).

- Rapidly progressive glomerulonephritis (RPGN) refers to glomerulonephritis progressing to renal failure within a short period of time (over days to weeks).

Etiology

Anti-GBM antibody disease
- Goodpasture's syndrome

Immune complex RPGN
- IgA nephropathy
- Post-streptococcal glomerulonephritis
- Lupus nephritis
- Membranoproliferative glomerulonephritis
- Mixed cryoglobulinemia

Pauci-immune RPGN
- Wegener's granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome

Pathology

- RPGN is characterized by presence of crescents in renal biopsy, hence also called crescentic glomerulonephritis. Crescents are formed by the accumulation of cells and extracellular material in the urinary space of glomerulus. These cells are parietal and visceral epithelia as well as inflammatory cells.
- RPGN can be classified into 3 types based on pathologic features:
  - *Anti-glomerular basement membrane (GBM) antibody disease*: Linear deposits of antibodies on immunofluorescence.
  - *Immune complex RPGN*: Granular deposits of immune complexes on immunofluorescence.
  - *Pauci-immune RPGN*: Few or no immune deposits on immunofluorescence.

Clinical Features

- Manifestations are usually insidious, with weakness, fatigue, fever, nausea, vomiting, anorexia, arthralgia, and abdominal pain.
- Patients with anti-GBM antibody disease (Goodpasture's syndrome) may have pulmonary hemorrhage, which can present with hemoptysis.
- Patients also complain of hematuria, oliguria, and generalized edema.

Investigations

- Urea and creatinine are elevated because of renal failure.
- Urine analysis shows nephritic pattern with hematuria, RBC casts, WBCs and proteinuria.
- *Serologic testing*: Includes anti-GBM antibodies (present in anti-GBM antibody disease); antistreptolysin O antibodies (post-streptococcal GN), anti-DNA antibodies, or cryoglobulins (immune complex RPGN); and ANCA titres (pauci-immune RPGN).
- Complement level is low in immune complex RPGN.
- Renal ultrasound shows normal-sized kidneys.
- Chest X-ray may show infiltrates in Goodpasture's syndrome and other vasculitides.
- Kidney biopsy shows presence of crescents.

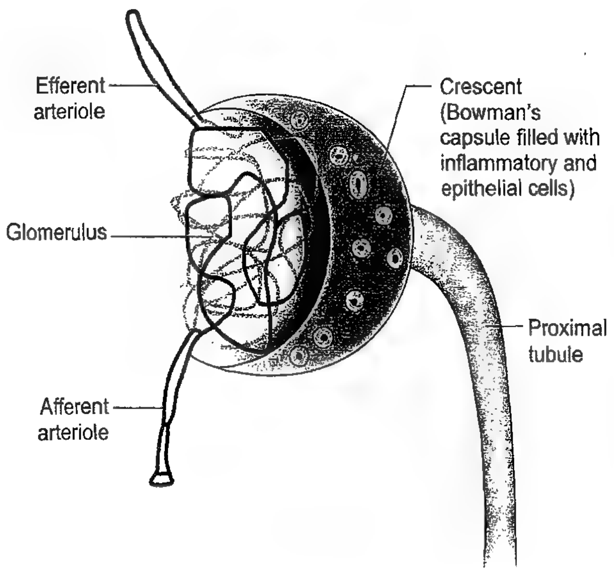

Fig. 8.3: Crescentic glomerulonephritis

Treatment

- Supportive therapy involves diuretics, antihypertensives and dialysis if required.

- For immune complex and pauci-immune RPGN, corticosteroids (methylprednisolone 1 g IV daily for 3 to 5 days followed by prednisone 1 mg/kg orally daily). Cyclophosphamide orally daily is added to prednisolone.
- Plasma exchange (daily 3- to 4-L exchanges for 14 days) is recommended for anti-GBM antibody disease.
- Kidney transplantation in end-stage renal disease.

Prognosis

- 80 to 90% of untreated patients progress to end-stage renal disease within 6 months.

Q. Tubulointerstitial nephritis (interstitial nephritis).

- Tubulointerstitial nephritis refers to inflammatory disease of renal tubules and the surrounding interstitium.

Etiology

Drugs (allergic)
- Penicillins, NSAIDs, allopurinol, lithium, cyclosporin

Autoimmune
- Sarcoidosis, Sjögren's syndrome, SLE

Infections
- Pyelonephritis, leptospirosis, tuberculosis, hantavirus

Toxic
- Myeloma light chains, mushrooms, Chinese herbs, lead

Metabolic and systemic diseases
- Hypokalemia, hypercalciuria, hyperoxaluria, amyloidosis

Congenital/developmental
- Vesicoureteric reflux, Wilson disease, medullary sponge kidney, sickle cell nephropathy

Clinical Features

- Tubulointerstitial nephritis can be acute or chronic. More than 95% of cases of acute tubulointerstitial nephritis result from infection or an allergic drug reaction. CTIN arises when chronic tubular insults cause gradual interstitial infiltration and fibrosis, tubular atrophy and dysfunction, and a gradual deterioration of renal function, usually over years.
- Acute tubulointerstitial nephritis may be asymptomatic. Fever, rash, arthralgias may be present in allergic (drug induced) interstitial nephritis. Some patients develop polyuria and nocturia due to a defect in urinary concentration and Na reabsorption.
- Chronic tubulointerstitial nephritis is usually asymptomatic unless renal failure develops.

Investigations

- Urea and creatinine are elevated.
- Hyperkalemia and acidosis may be present.
- Urine analysis shows proteinuria, hematuria, pyuria and eosinophils.
- Renal biopsy shows intense inflammation, with polymorphonuclear leucocytes and lymphocytes surrounding tubules and blood vessels and invading tubules (tubulitis), and occasional eosinophils (especially in drug-induced disease).

Management

- Underlying cause should be treated such as withdrawal of offending drug.
- Steroids (e.g. prednisolone 1 mg/kg/day) accelerate recovery and may prevent long-term scarring in allergic and autoimmune interstitial nephritis. Steroids should be given for 2 to 3 months.
- Supportive measures such as dialysis if required.

Q. Polycystic kidney disease (PKD).

- Polycystic kidney disease is a common disorder, occurring in approximately 1 in every 1000 live births. It is characterized by presence of extensive cysts scattered throughout both kidneys.
- There are 2 types of PKD. Infantile polycystic kidney disease and adult polycystic kidney disease. Infantile PKD is rare, autosomal recessive and usually fatal. Adult PKD is common and is inherited as autosomal dominant trait.

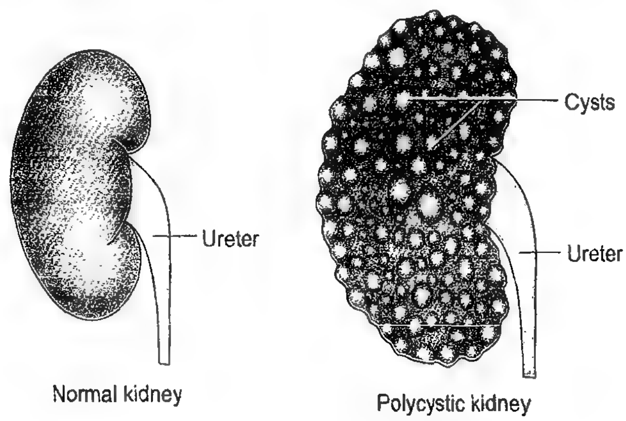

Fig. 8.4: Polycystic kidney disease

Pathogenesis

- Mutations in PKD1 and PKD2 genes are responsible for this disease.
- Small cysts lined by tubular epithelium develop from infancy or childhood and enlarge slowly compressing the normal kidney tissue leading to renal failure.

Clinical Features (Adult PKD)

- Patients are usually asymptomatic until later life.
- After the age of 20 there is often insidious onset of hypertension.
- Vague discomfort in loin or abdomen due to enlarged kidneys.
- Sometimes acute loin pain or renal colic due to hemorrhage into a cyst.
- One or both kidneys may be palpable and the surface may be nodular.
- Family history is usually positive.
- Gradual reduction in renal function.
- Some patients may have hepatic cysts, and berry aneurysms in the brain.
- Mitral and aortic regurgitation are also frequent in these patients.

Investigations

- Ultrasound abdomen shows multiple cysts in both kidneys.
- Urea and creatinine are elevated.

Management

- There is no treatment to alter the rate of progression of renal failure.
- Control of hypertension.
- Dialysis if required.
- Kidney transplantation in end-stage renal disease.

Q. Discuss the etiology, pathogenesis, clinical features, investigations and management of urinary tract infection.

- Urinary tract infection (UTI), defined as the bacterial invasion of the urinary tract. It can occur anywhere between the urethra and the kidney. UTI is the commonest of all bacterial infections.
- It is more common in women because of short urethra (4 cm) and up to 50% of women have a UTI at some time. UTI is uncommon in males except in the first year of life and in men over 60 because of prostate hypertrophy causing urinary obstruction.
- UTI causes morbidity and in some cases renal damage and chronic renal failure.
- UTI can present in following ways:
  - Asymptomatic bacteriuria: This is presence of bacteria in the urine without symptoms. It is common during pregnancy.
  - Symptomatic acute urethritis and cystitis
  - Acute pyelonephritis
  - Acute prostatitis
  - Septicemia
- Some patients, usually females, have symptoms of UTI without any bacteria in the urine. This is called urethral syndrome. This can occur due to infection with difficult to culture organisms (e.g. chlamydia, certain anaerobes), intermittent or very low-count bacteriuria, reaction to toilet preparations or disinfectants, symptoms related to sexual intercourse, or post-menopausal atrophic vaginitis. Antibiotics are not indicated for urethral syndrome.
- *Uncomplicated UTI* is cystitis or pyelonephritis that occurs in healthy, nonpregnant women without any structural abnormality of the urinary tract or comorbid illness that can increase the risk of complications.
- *Complicated UTI* can involve either sex at any age. It is pyelonephritis or cystitis which ocurs in patients with structural or functional urinary tract abnormality and obstruction of urine flow; patients with comorbid illness (e.g. diabetes); pregnant ladies and children; or after instrumentation of the urinary tract.

Etiology of UTI

Community acquired UTI

- *Escherichia coli* derived from GIT (75% of infections)
- Proteus
- Pseudomonas species
- Streptococci
- *Staphylococcus epidermidis*

Hospital acquired UTI

- *E. coli*
- Klebsiella
- Streptococci

Pathogenesis

- Most of the UTI (95%) are due to ascending infection from the urethra to bladder. Remaining are due to hematogenous spread of infection. The first step is colonization of the periurethral area with bacteria.
- Attachment of bacteria to the uroepithelial cells is an active process mediated by bacterial adhesins and receptors on the epithelial cells. Urothelium of susceptible persons may have more receptors to which virulent strains of *E. coli* become adherent. In women, the ascent of organisms into the bladder is easier than in men because of the relatively short urethra and absence of bactericidal prostatic secretions.
- Sexual intercourse and instrumentation of the bladder may also introduce organisms into the urethra and bladder.
- Multiplication of organism then depends on the size of the inoculum, virulence of the bacteria and host defences.

Risk Factors for UTI

Incomplete bladder emptying
- Bladder outflow obstruction (BPH, urethral stricture)
- Neurological problems (e.g. multiple sclerosis, diabetic neuropathy, myelopathy)
- Gynecological abnormalities (e.g. uterine prolapse)
- Vesicoureteric reflux

Foreign bodies
- Urethral catheter or ureteric stent

Loss of host defences
- Atrophic urethritis and vaginitis in post-menopausal women
- Diabetes mellitus

Clinical Features

- Increased frequency of micturition.
- Pain in the urethra during micturition (dysuria).
- Suprapubic pain during and after voiding (in cystitis).
- Urgency.
- Intense desire to pass more urine after micturition due to spasm of the inflamed bladder wall (strangury).
- Passing cloudy urine with unpleasant odor and occasionally hematuria.
- Systemic symptoms such as fever and chills may occur. Prominent systemic symptoms with fever and loin pain suggest acute pyelonephritis.

Investigations

- *Urine microscopy* shows presence of WBCs (>5 per high power field is significant) and RBCs. Bacteria also may be visible.
- Mid-stream urine culture and sensitivity. Growth of $>10^5$/ml organisms is regarded as significant.
- *Complete blood count* may show increased leukocyte count.
- Serum creatinine, blood urea and electrolytes may show evidence of renal failure.
- Renal ultrasound or CT to identify obstruction, cysts, or calculi.
- *Intravenous urogram (IVU)*: Alternative to ultrasound, particularly to image the collecting system after voiding.
- Pelvic examination in women with recurrent UTI to exclude cystocele, rectocele and uterovaginal prolapse.
- Rectal examination in elderly men to assess prostate.
- Intravenous urography for any anatomical/physiological anomalies.
- Micturating cystourethrography for vesicoureteric reflux.
- Cystoscopy in patients with hematuria or a suspected bladder lesion.
- Blood culture in septicemic cases.

Management

- Adequate fluid intake to maintain good urine ouput.
- Antibiotic therapy: The choice of antibiotic depends on the organism. Since the most common organism is *E.coli,* initial antibiotic therapy should be directed against this organism. Antibiotic choices are cotrimoxazole, amoxicillin, ampicillin, cephalosporins, quinolones and nitrofurantoin. Antibiotic should be modified once urine culture sensitivity reports are available. Duration of therapy is usually 3–5 days.
- Complicated UTI usually requires parenteral antibiotics for 7–14 days.
- Asymptomatic bacteriuria should be treated if the patient is pregnant or immunocompromised.
- Any underlying risk factor predisposing to UTI should be corrected such as BPH, cystocele, stones, etc.
- Alkalinization of urine with potassium citrate may help if there is severe dysuria.

Preventive Measures for Women with Recurrent UTI

- Fluid intake of at least 2 L/day
- Regular complete emptying of bladder
- If vesicoureteric reflux is present, practise double micturition (empty the bladder then attempt micturition 10–15 minutes later)
- Good perineal hygiene
- Emptying of the bladder before and after sexual intercourse

Q. Sterile pyuria.

- Sterile pyuria means presence of pus cells (WBCs) in the urine without apparent bacterial infection.

Causes

- Partially treated UTI
- Contamination of the urine sample by sterilizing solution
- Contamination of the urine sample with vaginal leukocytes
- Interstitial nephritis
- Calculi in the urinary tract
- Tuberculosis of the urinary tract
- Infection with difficult to culture organisms (Chlamydia)
- Bladder tumors
- Chemical cystitis
- Prostatitis
- Appendicitis

Q. Vesicoureteric reflux.

- Vesicoureteral reflux (VUR) is the retrograde passage of urine from the bladder into the upper urinary tract.

- It is the most common urologic anomaly in children, occurring in approximately 1% of newborns.
- VUR may transport bacteria from the bladder to the kidney leading to pyelonephritis. Recurrent pyelonephritis may lead to renal scarring, renal failure and hypertension.
- Diagnosis of VUR is made by demonstration of reflux of urine from the bladder to the upper urinary tract by either contrast micturiting cystourethogram or radionuclide cystogram.
- Treatment includes medical or surgical therapy. Medical treatment consists of prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole, trimethoprim alone, or nitrofurantoin. Surgical correction includes open surgical repair or endoscopic correction.

Q. Discuss the etiopathogenesis, clinical features, investigations and management of acute pyelonephritis.

- Pyelonephritis refers to infection of the renal parenchyma.
- Pyelonephritis is a serious infection and is less common than lower urinary tract infection (urethritis, cystitis).

Etiopathogenesis

- Pyelonephritis is usually due to ascending infection from the bladder. Rarely, it is due to hematogenous spread due to bacteremia. Common organisms are *E. coli, Klebsiella pneumoniae* and *Staphylococcus*.
- Pre-existing renal damage, such as cyst or scarring facilitates infection.
- The renal pelvis is inflamed and small abscesses may be present in the renal parenchyma. Histological examination shows focal infiltration by neutrophils, which can often be seen within the tubules.

Clinical Features

- Acute pyelonephritis presents as a classic triad of costovertebral angle (renal angle) pain, fever and tenderness over the kidneys.
- Costovertebral angle pain is usually acute onset, unilateral or bilateral and may radiate to the iliac fossa and suprapubic area. There may be associated tenderness and guarding in the lumbar region. Vomiting may be present.
- Fever is high grade with chills and rigors.
- Rarely, patients may present with sepsis, multiorgan dysfunction, hypotension, and acute renal failure.

Investigations

- Peripheral blood leukocytosis.
- Urine examination shows presence of pus cells (neutrophils), organisms, RBCs and tubular epithelial cells.
- Urine culture and sensitivity.
- Blood culture may sometimes growth causative organism.
- Renal ultrasound.
- CT scan may be required in doubtful cases.

Complications

- *Emphysematous pyelonephritis* commonly occurs in patients with diabetes. It is a severe, necrotizing form of pyelonephritis with gas formation and extension of the infection through the renal capsule.
- Renal and perinephric abscess formation.
- AKI.
- CKD.
- Sepsis with multiorgan dysfunction.

Management

- Adequate fluid intake, if necessary by intravenous route.
- *Antibiotic therapy*: For uncomplicated pyelonephritis, initial antibiotic choice can be oral trimethoprim-sulphamethoxazole or a fluoroquinolone. Intravenous ceftriaxone is another option if the patient is not able to take orally. For complicated pyelonephritis, broad-spectrum antibiotics such as piperacillin-tazobactam, cefepime, meropenem or imipenem should be given parenterally. Antibiotics should be modified based on culture sensitivity reports. Antibiotics should be given for 7–14 days.
- *Surgery* may be necessary if there is abscess formation.

Q. Renal replacement therapy.

Q. Hemodialysis.

Q. Peritoneal dialysis.

- Renal replacement therapy (RRT) replaces nonendocrine kidney function in patients with renal failure. RRT is also occasionally used for some forms of poisoning. Techniques of RRT include hemodialysis, peritoneal dialysis, hemofiltration, and kidney transplantation.
- Dialysis is based on the principle that solutes shift from high concentration compartment to low concentration compartment if separated by a semipermeable membrane. During dialysis, serum solute (e.g. urea, creatinine) diffuses passively between fluid compartments down a concentration gradient. In the context of dialysis, patient blood forms one compartment (contains high concentration of urea, creatinine) and dialysis fluid forms

another compartment separated by a semipermeable membrane. In hemofiltration, serum water passes between compartments down a hydrostatic pressure gradient, dragging solute with it. Both dialysis and hemofiltration can be done intermittently or continuously.

- Dialysis is of two types; hemodialysis and peritoneal dialsysis. Hemodialysis employs an artificial membrane through which patient blood is passed. Peritoneal dialysis is done by using the peritoneal membrane as the semipermeable membrane.

Indications for Dialysis

- Plasma urea >180 mg/dl and creatinine >6.8 mg/dl
- Hyperkalemia >6 mmol/L
- Metabolic acidosis
- Fluid overload and pulmonary edema
- Uremic pericarditis
- Uremic encephalopathy

Hemodialysis

- Hemodialysis is more efficient than peritoneal dialysis in removing urea and creatinine. In hemodialysis there is diffusion of solutes between plasma and dialysate fluid across a semipermeable membrane following a concentration gradient.
- Semipermeable membrane is made of cellulose, cellulose acetate or synthetic material (polymethyl methacrylate, polycarbonate).

Technique

- Blood from the patient is made to flow through the dialysis machine which contains a semipermeable membrane. This semipermeable membrane separates the blood and dialysis fluid. Solutes such as urea, creatinine and potassium shift from high concentration compartment (blood) to low concentration compartment (dialysis fluid) through the semipermeable membrane.
- Fluid is removed by applying negative pressure to the dialysate side (ultrafiltration). After passing through the dialysis machine blood goes back to the patient.
- Heparin is given to prevent clotting of the blood as it passes through the dialysis machine.
- Vascular access can be obtained by placing a catheter into the femoral or internal jugular vein. AV fistula can be created in the forearm for permanent vascular access.
- Initially hemodialysis is done for 1 hour to avoid sudden change in fluid and electrolyte balance in the patient. Subsequently hemodialysis is done for 3–4 hours 3–4 times a week.

Complications of Hemodialysis

- Nausea, vomiting, and headache.
- Hypotension due to fluid removal and hypovolemia.
- Cardiac arrhythmias due to sudden potassium and acid–base shifts.
- Hemorrhage due to anticoagulation.
- Air embolism due to disconnected or faulty lines and equipment malfunction.

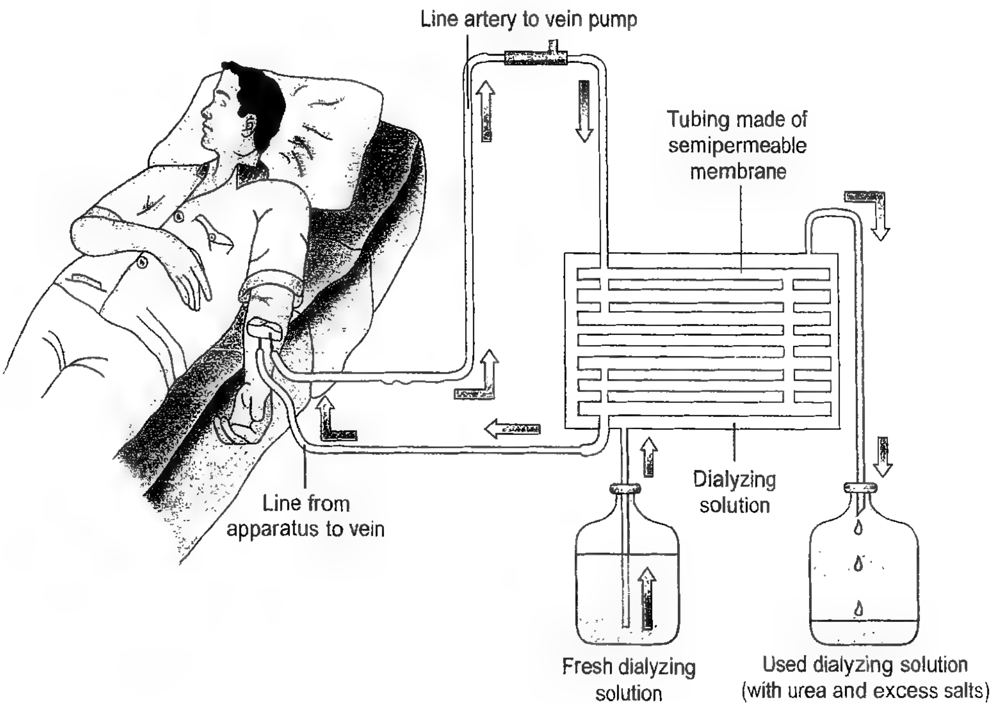

Fig. 8.5: Hemodialysis

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- Allergic reaction to dialysis membrane or sterilisant.
- Dialysis disequilibrium syndrome may follow a session of dialysis. It is due to cerebral edema which develops due to rapid decrease in plasma osmolality. It is characterized by nausea, vomiting, restlessness, headache, hypertension, myoclonic jerks and in severe cases seizures and coma.
- Cardiac disease has been found to be higher in patients on long-term hemodialysis.
- Dementia is more common in patients on long-term dialysis. Reasons for this may be other comorbid illness and age rather than dialysis itself. Dementia associated with aluminum intoxication in dialysis patients is now uncommon due to adoption of alternatives to aluminum-containing compounds as phosphate binders.

Peritoneal Dialsysis (PD)

- In peritoneal dialysis (PD), peritoneum acts as a semi-permeable membrane across which diffusion of solutes and water takes place.
- It is less efficient than hemodialysis, and is rarely used in AKI. It requires an intact peritoneal cavity and is not feasible after recent abdominal surgery.
- Access to the peritoneal cavity is obtained through a peritoneal catheter made of silicon rubber with numerous side holes at the distal end.
- 1.5–3 L of a dextrose-containing solution is infused into the peritoneal cavity and allowed to dwell for 2 to 4 hours. Uremic toxins diffuse from the peritoneum into the dialysis fluid during this period which is then removed and fresh dialysis fluid is infused.

Forms of PD

- PD can be done manually or using an automated device. In manual methods dialysis fluid is infused into the peritoneum manually and is drained manually. Automated PD uses an automated device to do multiple night time exchanges, sometimes with a daytime dwell.
- *Continuous ambulatory peritoneal dialysis (CAPD)*: Involves multiple exchanges during the day (usually four, but sometimes three or five) with an overnight dwell. The dialysate is infused into the abdomen at bedtime and is drained upon awakening.
- *Continuous cyclic peritoneal dialysis (CCPD)*: This is an automated form of therapy in which a machine performs exchanges while the patient sleeps; there may be a long daytime dwell, and occasionally a manual daytime exchange is performed. CCPD generally allows significantly more uninterrupted time for work, family, and social activities than CAPD.

Complications of Peritoneal Dialysis

- Peritonitis.
- Increased risk of hernias.
- Hyperglycemia due to use of dextrose containing fluid as the dialysis fluid.
- Weight gain due to glucose absorption from the dialysis fluid.
- Protein malnutrition.

Q. Dialysis disequilibrium syndrome.

- Dialysis disequilibrium syndrome is the occurrence of neurologic signs and symptoms, attributed to cerebral edema, during or following shortly after intermittent hemodialysis

Etiology

- Removal of urea from the blood by hemodialysis reduces osmolality of blood producing an osmotic disequilibrium between blood and brain. Since it takes sometime for the urea concentration in the brain to reduce, water moves into brain cells causing brain edema.
- Another mechnism postulated is during hemodialysis, existing systemic metabolic acidosis is promptly corrected, but the corresponding CSF pH level remains low. This produces brain edema by unknown mechanisms
- Disequilibrium syndrome most commonly occurs in first few dialysis sessions and in patients with high pre-dialysis urea.

Clinical Features

- Signs and symptoms of cerebral edema, such as focal neurological deficits, papilledema and decreased level of consciousness, occurring immediately after dialysis should raise the suspicion of DDS.

Investigations

- CT or MRI brain is required to rule out other neurological problems such as stroke, intracranial bleed, etc.
- Serum electrolytes.

Treatment

- Usually self-limited. However, for severe symptoms hemodialysis should be stopped.
- If seizures occur, antiepileptics should be given such as diazepam, and phenytoin.
- Brain edema can be reduced by IV mannitol and glycerol.

Prevention

- Initial sessions of dialysis should be short so as to gradually bring down the blood urea.

- Prophylactic administration of osmotically active agents (mannitol, glucose) and using high sodium dialysate in high risk patients.

Q. Renal transplantation.

- Kidney transplantation is the commonest organ transplantation done.
- It offers the best chance of long-term survival in patients with end-stage renal disease. It can restore normal kidney function and correct all the metabolic abnormalities of CKD.

Procedure

- Kidney grafts are taken from a cadaver or a living donor.
- ABO (blood group) and HLA antigens should be matched between the donor and recipient, otherwise failure of the transplant can occur due to graft rejection. Transplantation usually succeeds if all known class I (HLA-A, B, and C) and class II antigens (HLA-DR) between donor and recipient are matched.
- Patient should be dialyzed before transplantation to achieve a near normal metabolic state.
- Surgical technique: The new kidney is placed in one or the other iliac fossa, in an extraperitoneal position that allows ease of repeated biopsy to detect the cause of graft dysfunction. The renal artery is anastomosed to common iliac artery. Renal vein is anastomosed to common iliac vein. Ureter is implanted into the bladder. Patients own kidneys are left *in situ*.

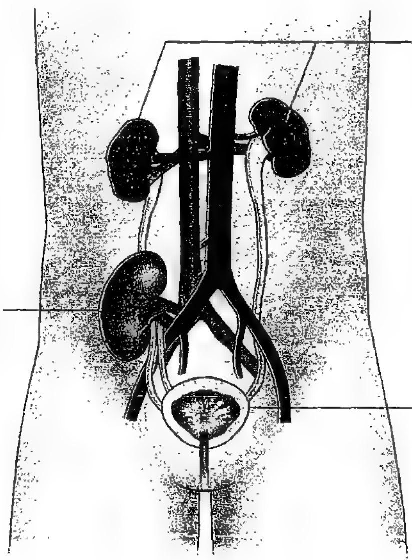

Fig. 8.6: Kidney transplantation

Management After Transplantation

- Immunosuppressive therapy is given to prevent graft rejection usually lifelong. A commonly used regimen is a combination of prednisolone, cyclosporin and azathioprine. Use of newer immunosuppressive drugs such as mycophenolate mofetil and rapamycin is increasing.
- Rejection is treated by short courses of high-dose steroids in the first instance. Anti-lymphocyte antibodies or plasma exchanges are used in resistant cases.
- All transplant patients require regular lifelong follow-up to monitor renal function and immunosuppression.

Complications

Peri-operative Problems

- Fluid imbalance. Careful matching of input to output is required.
- Primary graft non-function. Causes include hypovolemia, acute tubular necrosis, hyperacute rejection, vascular occlusion and urinary tract obstruction.

Complications due to Immunosuppression

- Increased risk of infections, especially opportunistic infections such as cytomegalovirus and *Pneumocystis carinii*.
- Increased risk of malignancy (skin cancer, lymphomas, etc.).
- Sepsis.

Contraindications to Renal Transplantation

Absolute

- Active malignancy
- Active vasculitis or anti-GBM disease
- Severe ischemic heart disease
- Severe occlusive aorto-iliac disease
- Persistent substance abuse
- Severe mental retardation
- Severe psychiatric disease

Relative

- Very young children (<1 year) or older people (>75 years).
- High risk of disease recurrence in the transplant kidney.
- Severe bladder or urethral abnormalities.
- Significant comorbidity.

Prognosis

- There is >75% patient survival and graft survival at 5 years.

Q. Renal tubular acidosis.

- Renal tubular acidosis (RTA) refers to the development of metabolic acidosis due to a defect in the kidney to reabsorb bicarbonate or to excrete hydrogen ions.

- All forms of RTA are characterized by a normal anion gap (hyperchloremic) metabolic acidosis.
- RTA should be suspected in patients with metabolic acidosis with normal anion gap or with unexplained hyperkalemia.

There are four major subgroups of RTA:

1. Type 1 RTA or distal RTA
2. Type 2 RTA or proximal RTA
3. Type 3 RTA or mixed RTA
4. Type 4 RTA or hypoaldosteronism

Type 1 RTA or Distal RTA

- Distal RTA is due to impaired hydrogen ion secretion in the distal tubule.

Causes

- Idiopathic, sporadic
- Familial
- Autoimmune disease with hypergammaglobulinemia, particularly Sjögren's syndrome, RA, SLE
- Kidney transplantation
- Nephrocalcinosis
- Medullary sponge kidney
- Chronic obstructive uropathy
- Drugs (mainly amphotericin B, ifosfamide, and lithium)
- Cirrhosis
- Sickle cell anemia

Features

- Urine pH is abnormally high (>5.5) inspite of systemic acidosis.
- ABG shows normal anion gap metabolic acidosis.
- Chronic acidosis leads to bone demineralization and hypercalciuria. Bone demineralization leads to rickets in children and osteomalacia in adults. Hypercalciuria may lead to nephrolithiasis.
- Hypokalemia is frequently seen in distal RTA and the exact reason for this is unknown.
- Plasma bicarbonate is usually below 15 mEq/L.

Treatment

- Alkali therapy (usually potassium citrate) improves both calcium and potassium balance, and prevents stones and nephrocalcinosis.

Type 2 RTA or Proximal RTA

- This is due to failure of proximal tubules to reabsorb filtered bicarbonate from the urine, leading to bicarbonate wasting and acidosis.

Causes

- Fanconi syndrome
- Light chain nephropathy due to multiple myeloma
- Drugs (acetazolamide, sulfonamides, ifosfamide, outdated tetracycline, or streptozocin)
- Heavy metals (lead, cadmium, mercury)

Features

- ABG shows normal anion gap metabolic acidosis. Since distal segments can reabsorb bicarbonate, plasma bicarbonate concentration is usually between 12 and 20 mEq/L.
- Urine pH is above 7.5 and there is bicarbonaturia when the serum bicarbonate concentration is raised to a normal level.
- Proximal RTA is commonly associated with generalized proximal tubular dysfunction called the Fanconi syndrome. In addition to bicarbonaturia, generalized proximal dysfunction causes glucosuria, phosphaturia, uricosuria, aminoaciduria, and tubular proteinuria. Loss of phosphate may lead to bone demineralization.

Treatment

- Supplementation of bicarbonate.

Type 3 RTA or Mixed RTA

- This is due to carbonic anhydrase II deficiency in both proximal and distal tubules. It has features of both type 1 and type 2 RTA. Additional fatures are osteopetrosis, cerebral calcification, and mental retardation.
- Treatment is same as that for type 1 and type 2 RTA.

Type 4 RTA or Hypoaldosteronism

- This is due to either aldosterone deficiency or tubular resistance to the action of aldosterone.
- Aldosterone stimulates the secretion of both hydrogen and potassium in the distal tubules. Hence, hypoaldosteronism causes retention of hydrogen ions leading to acidosis and retention of potassium leading to hyperkalemia.

Causes

Primary aldosterone deficiency

- Primary adrenal insufficiency
- Congenital adrenal hyperplasia, particularly 21-hydroxylase deficiency
- Isolated aldosterone synthase deficiency

Hyporeninemic hypoaldosteronism

- Diabetic nephropathy
- Volume overload

- Drugs (ACE inhibitors, NSAIDs, cyclosporin)
- HIV infection
- Obstructive uropathy

Aldosterone resistance

- Drugs which close the collecting tubule sodium channel (amiloride, spironolactone, triamterene, trimethoprim)
- Tubulointerstitial disease
- Pseudohypoaldosteronism
- Distal chloride shunt

Features

- Hyperkalemia.
- ABG shows normal anion gap metabolic acidosis.
- Urine pH is appropriate, i.e. below 5.5 in the presence of acidosis.
- Bicarbonate concentration is usually >17 mEq/L.

Treatment

- Aldosterone deficiency is treated with fludrocortisone.
- Hyperkalemia is conrolled by restricting dietary potassium and diuretics.

Q. Renal tuberculosis.

Q. Tuberculosis of urinary tract.

- Tuberculosis of the kidney is secondary to tuberculosis elsewhere due to hematogenous spread.
- Initially, lesions develop in the renal cortex; these may ulcerate into the renal pelvis and involve the ureters, bladder, epididymis, seminal vesicles and prostate.
- Kidney calcification and ureteric stricture are common.

Clinical Features

- Fever, malaise, night sweats, weight loss
- Hematuria (sometimes macroscopic)
- Loin pain
- Symptoms of bladder involvement (frequency, dysuria)
- Chronic renal failure due to urinary tract obstruction or destruction of kidney tissue.

Investigations

- WBCs (pyuria) are present in the urine but routine urine cultures are negative ('sterile pyuria'). Early morning urine specimens should be examined by special techniques of microscopy and culture to detect tuberculous bacilli.
- Cystoscopy to assess bladder involvement.
- Chest X-ray to look for pulmonary tuberculosis.
- Montoux test may be positive.
- Ultrasound and CT abdomen to assess kidneys and bladder.
- IVP to assess distortion of kidneys and ureteric strictures.

Treatment

- Anti-tuberculous therapy as for pulmonary tuberculosis.
- Surgery may be required to relieve urinary tract obstruction or to remove a severely infected kidney.

Q. Renal artery stenosis (RAS).

- Renal artery stenosis refers to narrowing of one or both renal arteries. >70% narrowing is associated with reduction of blood flow to kidneys.

Etiology

- Atherosclerosis (most common cause).
- Fibromuscular dysplasia.
- Vasculitis (Takayasu's, PAN).

Clinical Features

- Hypertension is present if RAS is unilateral. Hypertension is due to activation of the renin-angiotensin system in response to renal ischemia. Hypertension is severe, and may be difficult to control.
- Renal failure if RAS is bilateral.
- Evidence of vascular disease elsewhere especially in the legs.
- Deterioration of renal function with ACE inhibitors. This happens because ACE inhibitors or angiotensin II receptor antagonists block efferent arteriolar vasoconstriction which maintains glomerular filtration pressure in ischemic kidney.
- Repeated flash pulmonary edema.

Investigations

- *Ultrasound abdomen* shows asymmetry in kidney size in unilateral RAS and bilaterally shrunken kidneys in bilateral RAS.
- Renal artery Doppler can identify significant renal artery stenosis.
- Renal isotope scanning may show delayed uptake of isotope and reduced excretion by the affected kidney, but this is unreliable in the presence of renal impairment.
- Renal arteriography is the definitive test, but is invasive and carries the risk of contrast nephropathy.
- MR angiography and spiral CT angiography are non-invasive are being increasingly used.

Management

- Medical management with antihypertensives, low-dose aspirin and lipid-lowering drugs.
- Angioplasty, with placement of stents.
- Surgical resection of the stenosed segment and re-anastomosis.

Q. Renal cell carcinoma (RCC); renal adenocarcinoma.

- Renal cell carcinoma (RCC) is the most common malignant tumor of the kidney in adults. It is an adenocacinoma and arises from renal tubules.
- It can spread into the renal pelvis, causing hematuria, along the renal vein into the inferior vena cava and to perinephric tissues. Lymphatic spread occurs to para-aortic nodes, and blood-borne metastases can occur to anywhere in the body.

Risk Factors

- Smoking, which doubles the risk.
- Obesity.
- Excess use of phenacetin.
- Acquired cystic kidney disease in dialysis patients.
- Some familial syndromes, particularly von Hippel-Lindau disease.
- Exposure to certain radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products.

Clinical Features

- It is twice as common in males as in females. The peak incidence is between 50 and 70 years of age and it is uncommon before 40.
- Symptoms usually do not appear until late, when the tumor may already be large and metastatic.
- Most common manifestation is gross or microscopic hematuria.
- Loin pain, abdominal mass may be present.
- RCC may secrete many substances leading to various paraneoplastic syndromes. These include fever, hypercalcemia, anemia, thrombocytosis, neuropathy, etc.

Investigations

- *Ultrasound abdomen*: Distinguishes between solid tumor and simple renal cysts.
- *CT abdomen and chest*: Helps in knowing the extent and staging of tumor.
- Biopsy of the lesion.

Management

- Radical nephrectomy is performed wherever possible. This includes the removal of kidney, perirenal fascial envelope and ipsilateral para-aortic lymph nodes. Radical nephrectomy should be considered even when metastases are present, because this leads to reduction of systemic effects and regression of metastases.
- Some benefit has been seen with immunotherapy using interferon and interleukin-2.
- RCC is resistant to radiotherapy and chemotherapy.

Endocrinology and Diabetes Mellitus

9

Q. Enumerate the common presenting complaints of endocrine dysfunction.

Easy fatigability: Hypothyroidism, diabetes mellitus, hyperparathyroidism, hypogonadism, adrenal insufficiency, Cushing's syndrome.

Weight gain: Hypothyroidism, Cushing's syndrome.

Weight loss: Thyrotoxicosis, adrenal insufficiency, diabetes mellitus.

Amenorrhea/oligomenorrhea: Menopause, polycystic ovarian syndrome, hyperprolactinemia, thyrotoxicosis, premature ovarian failure, Cushing's syndrome.

Precocious puberty: Gonadotropin excess.

Delayed puberty: Hypopituitarism, hypogonadism.

Polyuria and polydipsia: Diabetes mellitus, diabetes insipidus, hyperparathyroidism, Conn's syndrome (due to hypokalemia).

Hypertension: Pheochromocytoma, Cushing's syndrome, hypothyroidism.

Hypotension, hypoglycemia: Adrenal insufficiency.

Heat intolerance: Thyrotoxicosis, menopause.

Palpitations: Thyrotoxicosis, pheochromocytoma.

Thyroid enlargement: Goiter, Graves' disease, Hashimoto's thyroiditis.

Prominence of eyes: Graves' disease.

Hirsutism: Idiopathic, polycystic ovarian syndrome, congenital adrenal hyperplasia, Cushing's syndrome.

Alopecia: Cushing's syndrome, hypothyroidism.

Galactorrhea: Hyperprolactinemia.

Loss of libido: Hypogonadism.

Visual dysfunction: Pituitary tumor.

Headache: Acromegaly, pituitary tumor, pheochromocytoma.

Muscle weakness (usually proximal): Thyrotoxicosis, Cushing's syndrome, hypokalemia (e.g. Conn's syndrome), hyperparathyroidism, hypogonadism.

Paresthesiae and tetany: Hypoparathyroidism.

Recurrent ureteric colic: Hyperparathyroidism (due to hypercalcemia leading to stones).

Coarsening of features: Acromegaly, hypothyroidism.

Q. Discuss briefly the anatomy of pituitary gland, hormones secreted and their functions.

Anatomy

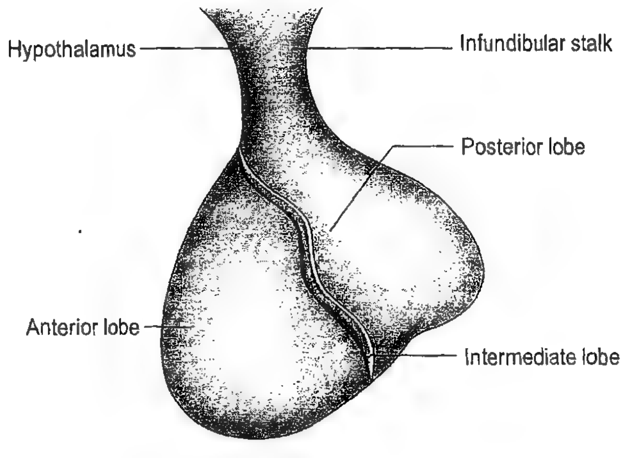

Fig. 9.1: Pituitary gland

- Pituitary gland lies within the sella turcica of the sphenoid bone and is bridged over by a fold of dura mater.
- Pituitary gland has a dual embryologic origin. The anterior lobe is formed from Rathke's pouch, and posterior lobe from the floor of the third ventricle.
- It is composed of two predominant lobes, anterior (adenohypophysis) and posterior (neurohypophysis) lobes. The intermediate lobe is rudimentary in humans.
- Important relations of the gland are sphenoid sinus anteroinferiorly, cavernous sinus (with internal carotid arteries and cranial nerves III, IV, V, and VI) laterally, and optic chiasma anterior to the pituitary stalk.
- The gland is connected to the hypothalamus by the infundibular stalk, which has portal vessels carrying blood from the median eminence of the hypothalamus to the anterior lobe and nerve fibers to the posterior lobe.

Hormones Secreted by Pituitary Gland and their Functions

Anterior pituitary hormones

- ***Growth hormone:*** Promotes growth; lipid and carbohydrate metabolism.
- ***Adrenocorticotropic hormone (ACTH):*** Stimulates adrenal glands to produce hormones such as cortisol and aldosterone important for stress response and fluid electrolyte balance.
- ***Thyroid-stimulating hormone (TSH):*** Stimulates the thyroid gland to release thyroid hormones. Thyroid hormones control basal metabolic rate and play an important role in growth and maturation.
- ***Follicle-stimulating hormone (FSH) and luteinizing hormone (LH):*** Growth of reproductive system and sex hormone production.
- **Prolactin:** Stimulates secretion of breast milk.

Posterior pituitary hormones

- ***Antidiuretic hormone (ADH):*** Conservation of body water.
- ***Oxytocin:*** Stimulates milk ejection and uterine contractions.

Q. Hypopituitarism; panhypopituitarism.

- Hypopituitarism refers to decreased secretion of pituitary hormones.
- It can result either from diseases of the pituitary gland, or diseases of the hypothalamus leading to deficiency of hypothalamic releasing hormones.

Causes of Hypopituitarism

Pituitary diseases

- Mass lesions—pituitary adenomas, cysts, metastatic cancer.
- Postpartum necrosis (Sheehan's syndrome)
- Pituitary surgery
- Pituitary radiation
- Hemorrhage
- Infiltrative lesions—hemochromatosis, lymphocytic hypophysitis
- Empty sella syndrome

Hypothalamic diseases

- Mass lesions, sarcoidosis, surgery, radiotherapy, tuberculosis, hemorrhage.

Clinical Features

- The clinical manifestations of hypopituitarism depend upon the cause as well as the deficiency of each anterior pituitary hormone.
- *Growth hormone deficiency*—it leads to short stature in children. In adults, it may result in diminished muscle mass, increased fat mass and diminished sense of well being.
- *TSH deficiency*—clinical features are due to accompanying thyroxine deficiency. Features are fatigue, lethargy, cold intolerance, decreased appetite, constipation, facial puffiness, dry skin, bradycardia, delayed relaxation of deep tendon reflexes, and anemia.
- *ACTH deficiency*—presentation is due to cortisol deficiency. This can be in the form of acute adrenal insufficiency characterized by hypotension. Mild, chronic deficiency causes fatigue, anorexia, weight loss, decreased libido, hypoglycemia, and eosinophilia.
- *Gonadotropin deficiency (FSH and LH)*—causes hypogonadism in both men and women. Women have ovarian hypofunction resulting in inability to ovulate, infertility, oligo- or amenorrhea, vaginal dryness and atrophy, and fatigue. Estradiol deficiency causes hot flashes. Men have testicular hypofunction, which results in infertility and decreased testosterone secretion. The latter causes decreased energy and libido and decreased bone mineral density.
- *Prolactin deficiency*—leads to inability to lactate after delivery.
- Patients with a pituitary or sellar mass may have symptoms related to the mass, such as headache, visual loss, or diplopia.

Investigations

- Low ACTH and low cortisol levels indicate pituitary problem. If cortisol is high and ACTH low, it indicates Cushing's disease and secondary suppression of ACTH.
- Low T4 and TSH indicates pituitary problem.
- Low serum testosterone and low LH indicate hypogonadism due to pituitary problem. Similarly in a woman, low estradiol and low FSH also indicate pituitary problem.
- Growth hormone level is low.
- CT or MRI of the head to identify pituitary pathology.

Treatment

- Treatment of hypopituitarism involves the treatment of each individual target gland hormone deficiencies.
- ACTH deficiency is treated by giving hydrocortisone or other glucocorticoid.
- TSH deficiency, which results in thyroxine deficiency, is treated with L-thyroxine.
- In men with gonadotropin deficiency, testosterone replacement is indicated when fertility is not desired. If fertility is desired, they are treated with gonadotropins. In women with gonadotropin deficiency, estrogen and progestin replacement is enough if fertility is not

desired. If fertility is desired, they should be treated with gonadotropin or pulsatile GnRH therapy to induce ovulation.

- Growth hormone is replaced with recombinant human growth hormone.

Q. Pituitary infarction (Sheehan's syndrome).

- Hypopituitarsim due to infarction of the pituitary gland after postpartum hemorrhage is called Sheehan's syndrome. The pituitary gland is physiologically enlarged in pregnancy and is therefore very sensitive to the decreased blood flow caused by massive hemorrhage and hypovolemic shock.
- In developed countries, Sheehan's syndrome is less common due to improved obstetrical care. However, in underdeveloped and developing countries, it remains a common cause of hypopituitarism.

Clinical Features

- Patients often have a history of severe postpartum hemorrhage causing hypotension and requiring blood transfusion.
- Severe hypopituitarism manifests during the first days or weeks after delivery. Less severe hypopituitarism manifests weeks or months after delivery.
- Failure to lactate or difficulties with lactation are common initial symptoms of Sheehan's syndrome (due to prolactin deficiency). Many women also report amenorrhea or oligomenorrhea after delivery (due to FSH and LH deficiency). Other features include fatigue, anorexia, weight loss (due to decreased ACTH), and features of hypothyroidism (due to decreased THS).

Investigations

- There is deficiency of all the hormones, i.e. growth hormone, prolactin, gonadotropins, TSH and ACTH.
- CT scan or MRI shows a small pituitary within a sella of normal size, sometimes read as an "empty sella".

Treatment

- Treatment is same as that for hypopituitarism.

Q. Enumerate the causes of short stature.

Normal variation of growth
- Familial short stature
- Constitutional delay of growth and puberty
- Idiopathic short stature
- Small for gestational age infants with catch-up growth

Systemic disorders with secondary effects on growth
- Undernutrition
- Glucocorticoid therapy
- Gastrointestinal disease (Crohn disease, celiac disease)
- Rheumatologic disease (juvenile rheumatoid arthritis, etc.)
- Renal disease (CKD)
- Cancer
- Pulmonary disease (cystic fibrosis, bronchiectasis)
- Cardiac disease (congenital heart disease)
- Metabolic diseases

Endocrine causes of growth failure
- Cushing's syndrome
- Hypothyroidism
- Growth hormone deficiency
- Vitamin D deficiency
- Precocious puberty

Genetic diseases with primary effects on growth
- Turner syndrome
- Prader-Willi syndrome
- Noonan syndrome
- Russell-Silver syndrome
- Skeletal dysplasias

Q. Discuss the etiology, clinical features, investigations, and management of acromegaly.

- Acromegaly is the clinical syndrome that results from excessive secretion of growth hormone (GH).
- If GH hypersecretion occurs before epiphyses have fused, then gigantism will result. If GH excess occurs in adult life, after epiphyseal closure, then acromegaly occurs. If hypersecretion starts in adolescence and persists into adult life, then the two conditions may be combined.
- The mean age at diagnosis of acromegaly is 40 to 45 years.

Etiology

- The most common cause of acromegaly is a somatotroph (growth hormone-secreting) adenoma of the anterior pituitary. Most of these are macroadenomas.
- Other causes of acromegaly are excess secretion of growth hormone-releasing hormone (GHRH) by hypothalamic tumors, ectopic GHRH secretion by nonendocrine tumors such as carcinoid tumors or small-cell lung cancers, and ectopic secretion of GH by nonendocrine tumors.

Clinical Features

- There is stimulation of growth of many tissues, such as skin, connective tissue, cartilage, bone, viscera, and many epithelial tissues.
- Findings include an enlarged jaw (macrognathia) and enlarged, swollen hands and feet. Facial features become coarse, with enlargement of the nose and frontal bones as well as the jaw, and the teeth become spread

apart. Macroglossia and enlargement of the soft tissues of the pharynx and larynx lead to obstructive sleep apnea.

- Skin thickness is increased and hyperhidrosis is common. Hair growth increases, and some women have hirsutism.
- Enlargement of synovial tissue and cartilage causes hypertrophic arthropathy of the joints.
- Fatigue and weakness can be prominent symptoms. They may result from sleep apnea, cardiovascular dysfunction, neuropathy, hypogonadism, and hyperglycemia.
- Cardiovascular abnormalities include hypertension, left ventricular hypertrophy, and cardiomyopathy.
- Pituitary adenoma may cause local symptoms such as headache, visual field defects (classically bitemporal hemianopsia) and cranial nerve palsies. It may also cause decreased secretion of other pituitary hormones due to its mass effect, most commonly gonadotropins. Many women with acromegaly have menstrual dysfunction, hot flashes and vaginal atrophy.
- There is increased risk of colon cancer and uterine fibroids.
- Mortality is increased in acromegaly due to cardiovascular diseases and cancer.

Investigations

- Measurement of GH levels during an oral glucose tolerance test. In normal subjects, plasma GH suppresses to below 2 mU/L. In acromegaly, it does not suppress and there may be a paradoxical rise. This test may not be helpful in diabetes patients as inadequate insulin secretion may fail to suppress GH. However, in diabetic patients with acromegaly, IGF-1 levels are high and low in patients without acromegaly.
- Blood glucose levels may be high due to excess growth hormone causing insulin resistance.
- Prolactin concentrations are elevated in about 30% of patients due to co-secretion of prolactin from the pituitary adenoma.
- CT or MRI of brain demonstrates pituitary adenoma.
- Skull X-rays disclose cortical thickening, enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica. X-rays of the hands show tufting of the terminal phalanges and soft-tissue thickening.
- Colonoscopy to screen for colonic neoplasms.

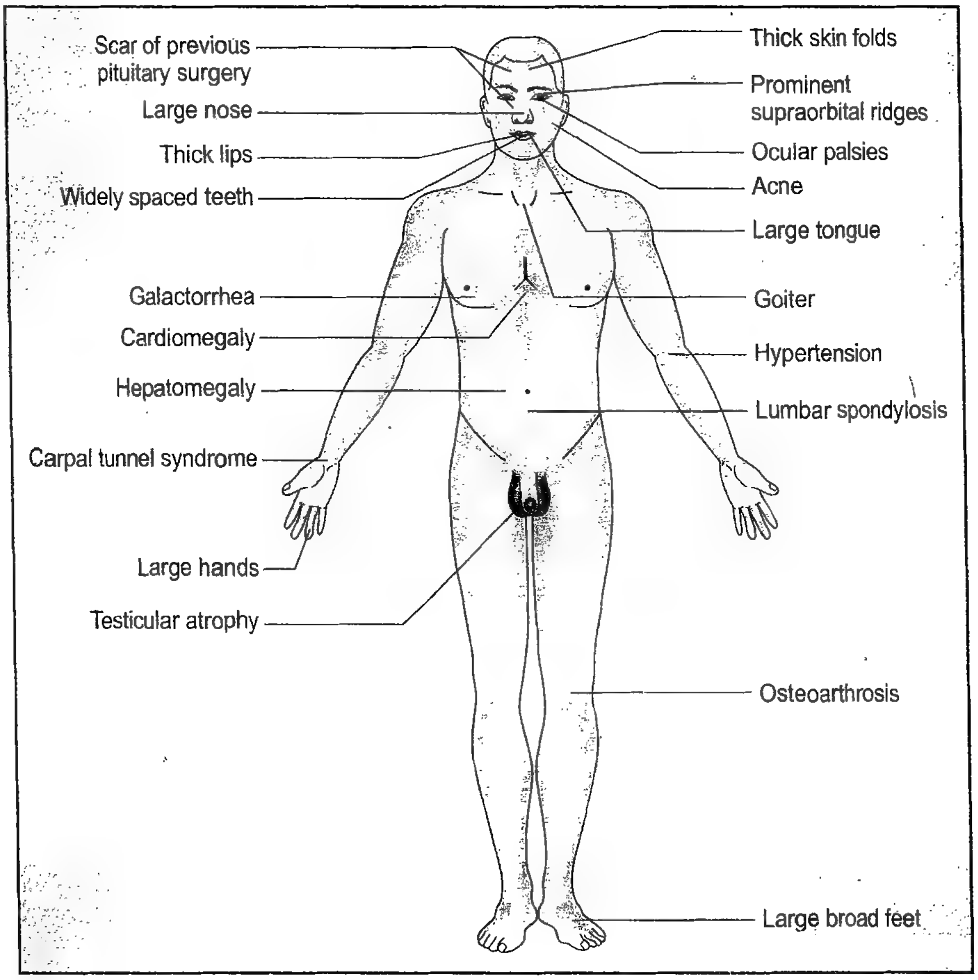

Fig. 9.2: Clinical features of acromegaly

Management

Surgical

- Trans-sphenoidal surgery to remove the adenoma is usually the first-line of treatment and may result in cure of GH excess. Surgery is also useful to debulk the tumor followed by second-line therapy.

Radiotherapy

- External radiotherapy is usually employed as second-line treatment if acromegaly persists after surgery.

Medical

- This may be employed in patients with persisting acromegaly after surgery. Agents which can suppress GH secretion are somatostatin analogues (e.g. octreotide or lanreotide), dopamine agonists (bromocriptine, cabergoline) and GH receptor antagonist (pegvisomant).

Q. Growth hormone deficiency.

Causes of Growth Hormone Deficiency

- These are same as the causes listed under hypopituitarism.

Clinical Features

- Growth hormone (GH) deficiency in children presents as short stature.
- Growth hormone deficiency in adults is associated with a decrease in lean body mass and an increase in fat mass.
- Other features are higher serum LDL cholesterol, impairment of cardiovascular function, decreased bone mineral density, feeling less healthy and less energetic than normal subjects, and reduced life expectancy.

Diagnosis

- Reduced serum IGF-1 or growth hormone levels.
- Provocative tests—a subnormal rise in the serum growth hormone concentration after insulin-induced hypoglycemia or after injection of combination of arginine and growth hormone-releasing hormone confirms the diagnosis of growth hormone deficiency.

Treatment

- Recombinant human GH preparations are available. GH is given as subcutaneous injection once a day, usually in the evening.
- All children with GH deficiency should receive recombinant growth hormone to normalize growth and development.
- Growth hormone should also be given to adult patients with severe clinical manifestations and unequivocal biochemical evidence of growth hormone deficiency.
- Dose of GH should be adjusted to maintain serum IGF-1 levels within the normal range.

Q. Hyperprolactinemia; prolactinoma.

Galactorrhea

- Hyperprolactinemia is a common biochemical abnormality.
- The cardinal features are galactorrhea and hypogonadism. Galactorrhea refers to lactation without breastfeeding. Prolactin stimulates milk secretion but not breast development, hence galactorrhea is not seen in men, but can occur if there is gynecomastia.
- Prolactinoma is an important cause of hyperprolactinemia. Most prolactinomas in pre-menopausal women are microadenomas, because they are detected early due to symptoms. In men and post-menopausal women, tumors are usually macroadenomas due to late presentation.

Causes of Hyperprolactinemia

Physiological
- Stress (e.g. post-seizure)
- Pregnancy
- Lactation
- Nipple stimulation
- Coitus
- Baby crying

Drugs
- Dopamine antagonists (phenothiazines and butyrophenones, antidepressants, metoclopramide, domperidone)
- Dopamine-depleting drugs (reserpine, methyl dopa)
- Oral contraceptive pill

Pathological
- Prolactinoma (usually microadenoma)
- Disconnection hyperprolactinemia (e.g. non-functioning pituitary macroadenoma)
- Polycystic ovarian disease (PCOD)
- Hypothalamic disease
- Hypothyroidism
- Pituitary tumor secreting prolactin and growth hormone
- Macroprolactinemia
- Renal failure
- Ectopic source

Clinical Features

- In women, there is galactorrhea and hypogonadism leading to secondary amenorrhea, anovulation and infertility.
- In men there is decreased libido, reduced shaving frequency and lethargy.
- There may be headache and visual field defects due to mass effect of prolactinoma.

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Investigations

- Pregnancy should be excluded by urine pregnancy test and ultrasound in all women of child-bearing age.
- Serum prolactin levels are raised.
- Thyroid function tests to exclude primary hypothyroidism causing TRH-induced prolactin excess.
- MRI or CT scan of head to exclude hypothalamic or pituitary tumor.
- Assessment of other pituitary hormones in patients with a macroadenoma.

Management

- Underlying cause of hyperprolactinemia should be corrected. Examples are stopping offending drugs, correcting primary hypothyroidism, etc. If this is not possible, dopamine agonist therapy (bromocriptine, cabergoline, quinagolide, pergolide) will normalize prolactin levels.
- Prolactinomas can be treated by the following ways:
  - *Medical*—dopamine agonist drugs (bromocriptine, cabergoline) are first-line therapy. Dopamine agonists not only lower prolactin levels, but shrink the majority of prolactin-secreting macroadenomas.
  - *Surgical*—surgical removal may be required if the tumor is large and invasive or the patient is unable to tolerate dopamine agonists. Tumor can be removed by trans-sphenoidal surgery.
  - *Radiotherapy*—external irradiation may be required for some macroadenomas to prevent regrowth if dopamine agonists are stopped.

Q. Diabetes insipidus (DI).

- Diabetes insipidus (DI) results from a deficiency of vasopressin (ADH) due to a hypothalamic-pituitary disorder (central DI) or from resistance of the kidneys to vasopressin (nephrogenic DI).
- The posterior lobe of the pituitary is the primary site of vasopressin storage and release, but vasopressin is synthesized within the hypothalamus.
- Diabetes insipidus (DI) is characterized by persistent excretion of excessive quantities of dilute urine, and by thirst.

Etiology

Central
- Idiopathic
- Structural hypothalamic or high stalk lesion
- Familial disease (DIDMOAD syndrome-association of diabetes insipidus with diabetes mellitus, optic atrophy, deafness)
- Neurosurgery or trauma
- Cancer (primary brain tumors, metastases)
- Hypoxic encephalopathy
- Infiltrative disorders (histiocytosis, sarcoidosis)
- Post-supraventricular tachycardia

Nephrogenic
- Genetic defects (vasopressin-2 receptor mutation, aquaporin-2 mutation, cystinosis)
- Metabolic abnormality (hypokalemia, hypercalcemia)
- Drugs (lithium, demeclocycline)
- Poisoning (heavy metals)
- Polycystic kidney disease

Clinical Features

- Polyuria and polydipsia—patient may pass 5–20 liters or more of dilute urine in 24 hours. Polyuria leads to excess thirst and polydypsia.
- Diabetes insipidus may lead to dangerous hypovolemia if the patient does not have access to water or there is impaired thirst mechanism.

Investigations

- Measurement of 24-hour urine volume and creatinine excretion. Urine is clear and of low specific gravity. Urine osmolality is usually less than plasma.
- Serum glucose, urea, calcium, potassium, and sodium.
- *Vasopressin challenge test*—desmopressin (an analogue of vasopressin) is given in an initial dose of 5–10 μg intranasally (or 1 μg subcutaneously or intravenously). Urine volume is measured for 12 hours before and 12 hours after administration. Serum sodium should be measured if the patient develops symptoms of hyponatremia. Patients with central diabetes insipidus notice a distinct reduction in thirst and polyuria; serum sodium stays normal except in some salt-losing conditions.
- *Water deprivation test*
  - This is done to confirm the diagnosis of diabetes insipidus, and differentiate central from nephrogenic causes.
  - Patient is adviced not to take any fluids and his body weight, urine volume, plasma and urine osmolality are monitored hourly.
  - In diabetes insipidus there is rise in plasma osmolality and sodium concentration. When plasma osmolality rises above 300 mOsm/kg, exogenous desmopressin (DDAVP) is given, 2 μg IM.
  - Diabetes insipidus is confirmed if plasma osmolality is >300 mOsm/kg with a urine osmolality <600 mOsm/kg. Central diabetes insipidus is confirmed if urine osmolality rises by at least 50% after DDAVP.
  - Nephrogenic diabetes insipidus is confirmed if desmopressin (DDAVP) does not concentrate the urine.

- MRI of the pituitary and hypothalamus to look for mass lesions.

Management

- Treatment of central diabetes insipidus is with desmopressin (DDAVP). Desmopressin is usually administered as a metered dose spray into the nose. In emergencies, desmopressin is given by intramuscular injection. The dose of desmopressin is adjusted to keep the plasma sodium concentrations and/or osmolality in the normal range. The main side effect of desmopressin is excess water retention and hyponatremia.
- Nephrogenic diabetes insipidus is treated by thiazide diuretics, amiloride, and NSAIDs (e.g. indomethacin).

Q. Thyroid function tests.

- Thyroid secretes T4 (thyroxine) and T3 (triiodothyronine) which is regulated by pituitary TSH. TSH secretion, in turn, is controlled through negative feedback by thyroid hormones. TSH secretion is regulated by thyroid releasing hormone (TRH) from hypothalamus.
- Thyroid function is assessed by one or more of the following tests:
  - Serum TSH concentration.
  - Serum total T3 and T4 concentration.
  - Serum free T3 and T4.
  - Uptake of radioactive iodine or technetium.

Serum TSH	Serum T3, T4	Interpretation
Normal	Normal	Euthyroid
Low	High	Hyperthyroidism
High	Low	Primary hypothyroidism
High	High	TSH-mediated hyperthyroidism
Low	Low	Central hypothyroidism

Radionuclide Thyroid Scanning

- Radionuclide scanning of thyroid using technetium-99 is useful in demonstrating the distribution and functioning of thyroid gland. Earlier, ^{131}I was being used which has largely been replaced by technetium-99 which closely mimics radioactive iodine. Technetium-99 is injected intravenously into the arm and images of the thyroid are obtained with gamma camera approximately 20 minutes later.
- Increased uniform radionuclide uptake is seen in Graves' disease. Toxic adenomas appear as focal areas of increased uptake, with suppressed uptake in the remainder of the gland. In toxic multinodular goiter, there are multiple areas of relatively increased or decreased uptake. Subacute thyroiditis is associated with very low uptake.
- Thyroid scanning is also used in the follow-up of thyroid cancer. After thyroidectomy and radioablation using radioactive iodine, there is diminished radionuclide uptake in the thyroid gland. Areas of uptake indicate residual or metastatic thyroid cancer tissue.

Tests to Determine the Etiology of Thyroid Dysfunction

- Antibodies against thyroid peroxidase (TPO) and thyroglobulin are positive in autoimmune thyroid disease. Almost all patients with autoimmune hypothyroidism, and up to 80% of those with Graves' disease, have TPO antibodies.
- TSH receptor antibodies (TRAb) are positive in Graves' disease.
- Serum thyroglobulin levels are elevated in all types of thyrotoxicosis except that caused by exogenous administration of thyroid hormone. Thyroglobulin levels are particularly high in thyroiditis. The main role for thyroglobulin measurement, however, is in the follow-up of thyroid cancer patients. After total thyroidectomy and radioablation, thyroglobulin levels should be undetectable; otherwise, it indicates incomplete ablation or recurrent cancer.

Q. Discuss the etiology, clinical features, investigations and management of hyperthyroidism.

- Hyperthyroidism is characterized by increased synthesis and secretion of thyroid hormones which leads to the hyper-metabolic state.

Causes of Hyperthyroidism

- Autoimmune thyroid disease
- Graves' disease
- Hashitoxicosis
- Toxic adenoma
- Toxic multinodular goiter
- TSH-mediated hyperthyroidism
- Human chorionic gonadotropin-mediated hyperthyroidism
- Exogenous thyroid hormone intake
- Struma ovarii
- Metastatic follicular thyroid cancer
- Drugs (excess of iodine, amiodarone)

Clinical Features

General

- Weight loss despite normal or increased appetite
- Heat intolerance

- Fatigue
- Goiter with bruit
- Single or multiple nodules may be present in the thyroid

GIT
- Diarrhea, hyperdefecation
- Anorexia
- Vomiting

CVS
- Systolic hypertension/increased pulse pressure
- Palpitations
- Sinus tachycardia
- Atrial fibrillation
- High output cardiac failure
- Angina

RS
- Exacerbation of asthma
- Dyspnea on exertion

Hematological
- Lymphadenopathy
- Normochromic normocytic anemia (due to increased plasma volume)

Nervous system
- Tremor
- Muscle weakness
- Periodic paralysis
- Hyper-reflexia
- Ill-sustained clonus
- Proximal myopathy
- Bulbar myopathy

Skin
- Increased sweating
- Pruritus
- Hair thinning, alopecia
- Palmar erythema
- Pretibial myxoedema
- Onycholysis
- Hyperpigmentation
- Vitiligo can occur in association with autoimmune thyroid disorders

Genitourinary system
- Amenorrhea/oligomenorrhea
- Infertility, spontaneous abortion
- Loss of libido, impotence
- Gynecomastia
- Urinary frequency and nocturia

Eyes
- Stare and lid lag
- Gritty feeling or pain in the eyes
- Excessive lacrimation
- Diplopia
- Loss of acuity
- Exophthalmos
- Periorbital and conjunctival edema
- Corneal ulceration
- Ophthalmoplegia
- Papilledema

Bone
- Osteoporosis (fracture, loss of height)

Psychiatric
- Anxiety, irritability, emotional lability, psychosis

- About one-third of elderly patients with hyperthyroidism may be apathetic, rather than having hyperactivity, tremor, and other symptoms of sympathetic overactivity (apathetic or masked hyperthyroidism). Tachycardia may be absent because of coexisting conduction abnormality.

Investigations

- Serum T3 and T4 are elevated.
- Serum TSH is low in primary thyrotoxicosis and high in TSH induced thyrotoxicosis.
- TSH receptor antibodies (TRAb) are elevated in Graves' disease.
- Anti 6-thyroid peroxidase (anti-TPO) antibody titers are significantly elevated in Graves' disease, and usually are low or absent in toxic multinodular goiter and toxic adenoma.
- Isotope scanning may show increased or decreased uptake depending on the cause. Increased uptake is seen in Graves' disease. Decreased uptake is seen in thyroiditis. Radio-iodine uptake tests have been largely superseded by 99m technetium scintigraphy scans which are quicker to perform with a lower dose of radioactivity, and provide a higher resolution image.
- Thyroid ultrasound can identify nodules and distinguish solid from cystic lesions. Ultrasound-guided FNAC helps in obtaining cytologic material from nodules that are difficult to identify by palpation.

Management

- Definitive treatment of thyrotoxicosis depends on the underlying cause and may include antithyroid drugs, radioactive iodine or surgery.

Antithyroid Drugs

- These drugs decrease the thyroid hormone synthesis and release from thyroid gland. The thionamide derivatives, propylthiouracil (PTU), methimazole and carbimazole are the drugs of first choice in Graves' disease. These drugs interfere with organification and iodotyrosine coupling by inhibiting the peroxidase enzyme.
- These drugs are rapidly absorbed from GIT and concentrated in the thyroid. PTU inhibits peripheral conversion of T4 to T3, contributing 10 to 20% to the decrease in T3 levels. This effect is not seen with methimazole and carbimazole. Both PTU and methimazole cross the placenta and can interfere with fetal thyroid function. PTU can cause hepatic failure and hence, used only in first trimester of pregnancy.

- Methimazole is started at a dose of 5 to 10 mg OD. Improvement of thyrotoxic symptoms usually takes 2 to 3 weeks. Thyroid hormone values are checked 4 weeks after the start of therapy and if there is no improvement in thyroid function tests, the dose may be increased to 30 to 40 mg a day. Once thyroid hormone levels normalize, the dose is decreased. Most patients can be maintained on low doses of 2.5 to 5 mg of methimazole.
- PTU is given at a dose of 100 to 150 mg every 8 hours.
- The most important side effect of antithyroid drugs is agranulocytosis. Patients should be told to discontinue their medication and contact their physician when fever occurs or infection develops, especially in the oropharynx. If agranulocytosis develops, antithyroid drugs should be discontinued and broad-spectrum antibiotics should be given. Other treatment modalities such as radioactive iodine should be chosen for further treatment.

Radioactive Iodine

- Radioactive iodine (^{131}I) is used to treat hyperthyroidism in older patients with moderate hyperthyroidism and thyroid enlargement, for patients with a prior allergic or toxic reaction to the antithyroid medication, poor compliance with antithyroid drugs and after antithyroid drugs have failed to induce a long-term euthyroid state.
- Radioiodine treatment is contraindicated during pregnancy and pregnancy should be avoided for 6 to 12 months after radioiodine treatment.
- Antithyroid drugs should be stopped for 3 or 4 days before radioiodine administration. A dose of 5 to 10 mCi is usually required. Improvement in thyrotoxicosis occurs after 4 to 5 weeks, and almost 80% of patients are cured with one dose. The remaining need a second dose, which should be given 6 months after the first dose. After giving radioactive iodine, antithyroid drugs can be added at day 5 to reach a euthyroid state more quickly. Beta blockers are also used for symptomatic control.
- Rarely radioiodine can induce painful thyroiditis and lead to thyroid storm. Hypothyroidism is a risk and more than 50% of patients become hypothyroid after radioiodine treatment.

Surgical Therapy

- Subtotal thyroidectomy can be used to treat hyperthyroidism in the following situations:
  - Patients with large goiter causing obstructive symptoms.
  - Malignant thyroid nodule.
  - Pregnant women with severe hyperthyroidism, which is difficult to control with antithyroid drugs.
  - Young patients who are difficult to control on antithyroid drugs.
  - Patients with toxic reactions to antithyroid drugs.
  - Patients who are not candidates for antithyroid drugs and refuse radioactive iodine.
- However, hyperthyroidism should be controlled before surgery using PTU or methimazole. Thyroid surgery is contraindicated in severely hyperthyroid patients.

Symptomatic Treatment

- In all patients with thyrotoxicosis a non-selective β-blocker such as propranolol or nadolol should be used to control symptoms such as tachycardia, palpitations and tremors.

Q. Discuss the etiology, pathogenesis, clinical features, investigations and management of Graves' disease.

- Graves' disease, first described by Robert Graves' is a syndrome that consists of hyperthyroidism, goiter, ophthalmopathy and occasionally infiltrative dermopathy (pretibial myxedema).
- The terms Graves' disease and hyperthyroidism are not synonymous, because some patients with Graves' disease have ophthalmopathy but no hyperthyroidism.

Etiology and Pathogenesis

- Graves' disease is most likely an autoimmune disorder and is caused by autoantibodies to the TSH receptors (TSHR-Ab) that activate the receptor, thereby stimulating thyroid hormone synthesis and secretion as well as thyroid growth (causing goiter). These antibodies are produced by B lymphocytes.
- Infiltrative ophthalmopathy and dermopathy are specific to Graves' disease and are due to immunologically mediated activation of fibroblasts in extraocular muscles and skin, with accumulation of glycosaminoglycans leading to water trapping and edema initially, followed by fibrosis later.
- There is a genetic predisposition for Graves' disease as evidenced by strong association of Graves' disease with HLA-B8, DR3 and DR2, and high concordance rate in monozygotic twins. Viral and bacterial infections have been suspected to trigger the development of thyrotoxicosis in genetically susceptible individuals. *Escherichia coli* and *Yersinia enterocolitica* possess cell membrane TSH receptors; antibodies to these microbial antigens may cross-react with the TSH receptors on the host thyroid follicular cell.
- Iodine supplementation in iodine deficient areas can trigger the development of thyrotoxicosis in those with pre-existing subclinical Graves' disease.
- Histologic examination of the thyroid gland shows follicular hyperplasia, and patchy lymphocytic infiltration.

Clinical Features

- These are same as that discussed under hyperthyroidism.
- Features specific to Graves' disease are ophthalmopathy and infiltrative dermopathy (pretibial myxedema).
- Ophthalmopathy leads to proptosis and lid retraction preventing complete eye closure of the eyes, resulting in exposure keratitis and corneal ulceration. Compression of the optic nerve at the posterior apex by enlarged muscles may lead to blurring and impaired visual acuity, visual field defects, impairment of color vision, and papilledema.
- Treatment of ophthalmopathy involves prevention of drying and infection of the cornea by applying artificial tears and antibiotic drops. Surgical decompression may be required in severe proptosis with optic nerve compression.

Investigations and management of Graves' disease is same as that discussed under hyperthyroidism.

Q. Pretibial myxedema (infiltrative dermopathy).

- Infiltrative dermopathy (localized myxedema) is seen in Graves' disease and is less common than ophthalmopathy. It can also occur in patients with chronic autoimmune thyroiditis.
- The incidence of infiltrative dermopathy has declined due to earlier diagnosis and treatment of Graves' disease.

Pathology and Pathogenesis

- Infiltrative dermopathy occurs due to the accumulation of glycosaminoglycans, especially hyaluronic acid in the dermis. Characteristic pathologic changes are mucinous edema and the fragmentation of collagen fibers.
- The exact cause of infiltrative dermopathy is not proven. These patients have higher serum concentrations of TSH receptor antibodies than patients without dermopathy. TSH-receptors have been found in skin fibroblasts. TSH-receptor antibodies probably act on these receptors and stimulate the production of glycosaminoglycans.

Clinical Features

- Nonpitting scaly thickening and induration of the skin in the form of papules or nodules. They may be violaceous or slightly pigmented, and often have an orange-peel appearance.
- Pretibial areas of lower leg are most commonly affected. Rarely the fingers and hands, elbows, arms or face are affected.

Treatment

- Most patients are asymptomatic and do not require treatment. Indications for treatment are pruritus, local discomfort, or the unsightly appearance.
- The only effective treatment is topical application of a glucocorticoid ointment covered by an occlusive dressing (e.g. 0.02% fluocinolone under plastic wrap) at night. Resistant lesions may require systemic glucocorticoid therapy.

Q. Thyrotoxic crisis ('thyroid storm').

- This is a life-threatening increase in the severity of the clinical features of thyrotoxicosis. It is the most extreme state of thyrotoxicosis and is a medical emergency.
- It is rare and occurs in patients with Graves' disease or toxic multinodular goiter.

Precipitating Factors

- Infection.
- Trauma to the thyroid gland.
- After subtotal thyroidectomy in an ill-prepared patient.
- After radioiodine therapy.

Clinical Features

- Hyperpyrexia.
- Agitation, confusion, psychosis, stupor, or coma.
- Tachycardia, atrial fibrillation and cardiac failure.
- Severe nausea, vomiting, or diarrhea, and hepatic failure with jaundice.

Investigations

- Elevated T3, T4 and suppressed TSH levels. Rarely TSH may be elevated in instances of excess TSH secretion.
- CBC shows mild leukocytosis, with a shift to the left.
- LFTs show elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
- ECG may show arrhythmias such as atrial fibrillation.

Treatment

- Rehydration and antibiotics.
- Beta blockers to control symptoms of sympathetic overactivity. Propranolol can be given orally (80 mg 6 hourly) or intravenously (1 to 5 mg 6 hourly).
- Iodine compounds (Lugol iodine or potassium iodide) orally inhibit the peripheral conversion of T4 to T3 and also the release of thyroid hormones. Iodinated radiocontrast such as sodium ipodate can be given intravenously if available and is more effective than potassium iodide or Lugol's solution.
- Carbimazole 40–60 mg daily or propylthiouracil 200 mg of every four hours inhibits the synthesis of new thyroid hormone. Propylthiouracil is preferred over methimazole for treatment of severe thyroid storm because of its early onset of action and capacity to inhibit peripheral

conversion of T4 to T3. If the patient is unconscious these drugs can be given through Ryle's tube. Both drugs can also be suspended in liquid for rectal administration. Parenteral preparations of these drugs are not available.

- Glucocorticoids reduce conversion of T4 to T3. Dexamethasone (2 mg 6 hourly) is given.

Q. Subacute thyroiditis (giant cell thyroiditis; de Quervain's thyroiditis).

- Subacute thyroiditis is an acute inflammatory disease of the thyroid probably caused by a virus. It is characterized by neck pain, tender goiter, and thyroid dysfunction.

Etiology

- Subacute thyroiditis is presumed to be caused by a viral infection (coxsackievirus, mumps, measles, adenovirus) or a post-viral inflammatory process. The resulting thyroid inflammation releases thyroid hormones leading to thyrotoxicosis. Initial hyperthyroidism is sometimes followed by a transient period of hypothyroidism. The disease usually resolves spontaneously within months.

Clinical Features

- Pain in the thyroid, which may radiate to the neck or ears. Thyroid gland is enlarged and tender. Fever, fatigue, malaise, anorexia, and myalgia are common.

Investigations

- ESR is high.
- Technetium-99 uptake is low.
- Serum thyroglobulin is raised.
- Initially hyperthyroidism is seen, followed by euthyroidism, hypothyroidism and ultimately restoration of normal thyroid function.

Treatment

- Anti-inflammatory agents (NSAIDs or steroids) are used to control inflammation.
- Beta blockers (propranolol) are used to control thyrotoxic symptoms.

Q. Enumerate the causes of hypothyroidism.

Q. Discuss the clinical features, diagnosis, and management of primary hypothyroidism.

Etiology of Hypothyroidism

Primary hypothyroidism

- Chronic autoimmune (Hashimoto's) thyroiditis
- Iatrogenic (thyroidectomy, radioiodine therapy or external irradiation)
- Iodine deficiency or excess
- Drugs (thionamides, lithium, amiodarone)
- Infiltrative diseases (fibrous thyroiditis, hemochromatosis, sarcoidosis)
- Congenital causes (thyroid agenesis, dysgenesis, or defects in hormone synthesis)

Secondary (central) hypothyroidism

- TSH deficiency
- TRH deficiency

Thyroid hormone resistance

Primary Hypothyroidism

- Primary hypothyroidism refers to hypothyroidism caused by disease of the thyroid gland itself. Decreased secretion of T3 and T4 leads to a compensatory increase in TSH secretion. Thus, the combination of a low serum T3, T4 and a high serum TSH concentration indicates primary hypothyroidism.
- Two forms of primary hypothyroidism can be recognized:
  - *Subclinical hypothyroidism* is defined as a high serum TSH concentration in the presence of normal serum free T4 and T3 concentrations. These patients are usually asymptomatic.
  - *Overt hypothyroidism* is defined as a high serum TSH concentration in the presence of a low serum free T4 concentration. These patients are usually symptomatic.

Clinical Features

General

- Weight gain, fatigue, somnolence, cold intolerance, hoarseness of voice, slurred speech, puffy face and loss of eyebrows.

Skin

- Dry, cold and pale skin, decreased sweating, nonpitting edema (myxedema), carotenemia, coarse hair and hair loss, xanthelasma.

Hematologic

- Anemia, macrocytosis.

CVS

- Diastolic hypertension, bradycardia, reduced cardiac output, angina, pericardial effusion.

RS

- Hypoventilation, sleep apnea, exertional dyspnea, pleural effusion.

GIT

- Enlargement of the tongue, constipation (due to decreased gut motility), ileus, decreased taste sensation, ascites.

Reproductive system

- Oligomenorrhea, amenorrhea or menorrhagia, decreased fertility, increased risk of abortion, decreased libido, erectile dysfunction, delayed ejaculation.

Neuropsychiatric

- Encephalopathy, myxedema coma, mental retardation in children, carpal tunnel syndrome, cerebellar ataxia, depression, psychosis, myotonia, delayed relaxation of tendon reflexes.

Musculoskeletal

- Slow movement, myalgia, arthralgia, aches and stiffness.

Metabolic

- Hyperuricemia, hyponatremia, hyperlipidemia.

Investigations

- Serum T3, T4 is low and TSH elevated (>5).
- Serum cholesterol, triglycerides, lactate dehydrgenase (LDH), creatinine kinase (CK) and AST may be raised.
- Serum sodium levels may be low.
- Chest X-ray may show cardiomegaly.
- ECG may show sinus bradycardia with low voltage complexes and ST segment and T wave abnormalities.

Treatment

- Hypothyroidism is treated with levothyroxine (T4), with doses ranging from 50 to 200 µg/day. It is given once a day. Most patients require lifelong treatment and periodic evaluations should be done.
- In young healthy adults without coronary artery disease, a starting dose of 75 to 100 µg/day can be used and then every 4 weeks to reach the final replacement level. In elderly patients and those with coronary artery disease, the initial dose should be 12.5 to 25 µg/day and increased by 25 to 50 µg every 4 weeks to avoid precipitating angina and heart failure.
- The aim is to achieve a euthyroid status with TSH, T4, and T3 levels in the normal range. TSH is the most sensitive indicator and treatment should be aimed at normalizing TSH level.

Q. Hashimoto's thyroiditis (autoimmune thyroiditis; chronic lymphocytic thyroiditis).

- Hashimoto's thyroiditis is chronic autoimmune inflammation of the thyroid with lymphocytic infiltration. It is the most common cause of hypothyroidism in iodine-sufficient areas of the world.
- Hashimoto's thyroiditis, like Graves' disease, is sometimes associated with other autoimmune disorders, including Addison disease (adrenal insufficiency), type 1 diabetes mellitus, hypoparathyroidism, vitiligo, pernicious anemia, and connective tissue disorders (e.g. RA, SLE, Sjögren's syndrome).

Clinical Features

- More common in women.
- Diffuse goiter with characteristic firm or rubbery consistency.
- Features of hypothyroidism are present.

Investigations

- Thyroid function tests suggest hypothyroidism.
- Anti-TPO (anti-thyroid peroxidase) and anti-Tg (anti-thyroglobulin) antibodies are present in the serum in >90% of patients with Hashimoto's thyroiditis.
- Biopsy shows profuse lymphocytic infiltration, lymphoid germinal centers, destruction of thyroid follicles and fibrosis.

Treatment

- Thyroxine corrects hypothyroidism as well as helps in goiter shrinkage.

Q. Myxedema coma; myxedema madness.

- Myxedema coma is defined as severe hypothyroidism leading to decreased mental status, hypothermia, and other symptoms. Myxedema also refers to a dermatologic condition (pretibial myxedema), which occurs in hyperthyroidism and should not be mistaken for myxedema coma.
- Myxedema coma is a medical emergency with a high mortality rate.
- Older women are most often affected.
- Usual precipitating factors are infection, myocardial infarction, cold exposure, or sedative drugs, especially opiates.

Clinical Presentation

- The hallmarks of myxedema coma are decreased mental status and hypothermia.
- Most patients present with confusion and obtundation. Some may present with prominent psychotic features (myxedema madness). Untreated, patients will progress to coma.
- Other features are hypotension, bradycardia, hyponatremia, hypoglycemia, and hypoventilation.
- There may be evidence of a precipitating event such as infection, but fever may be absent in these patients.

Management

- Patient should be admitted to ICU.
- Treatment should be started without waiting for lab reports. Before thyroid hormone is given, however, blood should be drawn for measurements of T3, T4, TSH and cortisol to exclude associated adrenal insufficiency or hypopituitarism.

Thyroid Hormone Administration

- 300 µg thyroxine is given intravenously over 5–10 minutes initially, followed by 100 µg per day until patient becomes alert and able to take thyroxine orally. If no IV preparation is available same dose may be given through Ryle's tube.

Supportive Measures

- Hydrocortisone, 100 mg IV bolus followed by 100 mg every eight hours till associated adrenal insufficiency is excluded.
- Cover with blankets to correct hypothermia.
- Intravenous fluids, electrolytes, and glucose to correct electrolyte abnormalities and hypoglycemia.
- Mechanical ventilation if required.
- Treat precipitating factors (infection).
- Avoid sedatives and narcotics.

Q. Simple goiter.

- Simple goiter refers to diffuse enlargement of the thyroid with the patient in euthyroid state. It occurs sporadically and the etiology is unknown.

Clinical Features

- Usually presents between the ages of 15 and 25 years, often during pregnancy.
- There may be a tight sensation in the neck, particularly while swallowing.
- The goiter is soft, diffuse and the thyroid is enlarged to two or three times its normal size. There is no tenderness, lymphadenopathy or overlying bruit.

Investigations

- Thyroid function tests are normal. Thyroid autoantibodies are absent.

Treatment

- No treatment is necessary and in most cases the goiter regresses. In some cases, it may progress to become multinodular with areas of autonomous function.

Q. Endemic goiter.

- This is seen in areas of iodine deficiency. It presents as diffuse thyroid enlargement with the patient in euthyroid state.
- Thyroid function tests are normal. Serum inorganic iodide levels and urinary iodide excretion are low.
- Prevention involves fortification of common salt with iodine and intramuscular injection of 3 to 4 ml of iodized oil once in 2 years.

Q. Multinodular goiter.

- This refers to multinodular enlargement of the thyroid. Etiology is unknown.

Clinical Features

- Patients usually present with thyrotoxicosis.
- The goiter is large, nodular and may extend retrosternally.
- It may cause stridor due to tracheal compression, dysphagia due to esophageal compression, and hoarseness due to recurrent laryngeal nerve compression. It may also cause obstruction of the superior vena cava.

Investigations

- Ultrasound of the thyroid.
- Radioisotope thyroid scan.
- Chest X-ray and CT or MRI of the thoracic inlet to quantify the degree of tracheal compression and the extent of retrosternal extension.
- FNAC is indicated in those with a 'dominant', 'cold' nodule, to exclude thyroid cancer.

Management

- No treatment is required if the goiter is small and patient is euthyroid. However, patients should be followed up yearly as it may progress to toxic multinodular goiter.
- Partial thyroidectomy is indicated for large goiter causing mediastinal compression or for cosmetic reasons. Iodine-131 (also known as radio iodine) can result in a significant reduction in thyroid size and may be of value in elderly patients.
- Iodine 131 is used for toxic multinodular goiter.

Q. Enumerate the causes of hyperparathyroidism.

Q. Discuss the etiology, clinical features, investigations and management of primary hyperparathyroidism.

Causes of Hvperparathyroidism

Primary
- Adenoma, glandular hyperplasia, familial hyperparathyroidism (as part of multiple endocrine neoplasia), carcinoma

Secondary
- Hypocalcemia due to any reason may stimulate parathyroid glands leading to secondary hyperparathyroidism, e.g. CKD, malabsorption, osteomalacia.

Tertiary
- The secondarily stimulated parathyroid glands as in CKD may enlarge, becoming autonomous leading to tertiary hyperparathyroidism.

Primary Hyperparathyroidism

- Primary hyperparathyroidism is due to a problem in the parathyroid glands themselves. It is characterized by excessive secretion of PTH by one or more parathyroid glands.
- It can be seen at any age but is more frequent in persons over the age of 50 years and is three times more common in women than men.

Etiology

- See above.

Clinical Features

Manifestations of Hypercalcemia

- See under hypercalcemia.

Skeletal Manifestations

- Bone demineralization and loss of cortical bone.
- Severe cases progress to osteitis fibrosa cystica.
- Pathologic fractures.
- Bone pain and arthralgias.

Urinary Tract Manifestations

- Polyuria and polydipsia due to hypercalcemia-induced nephrogenic diabetes insipidus.
- Kidney stones due to hypercalciuria.
- Urinary tract infection due to stone and obstruction may lead to renal failure and uremia.

Hyperparathyroidism During Pregnancy

- Fetal demise, preterm delivery, low birth weight, postpartum neonatal tetany.

Investigations

- Hypercalcemia is the most important finding. Serum calcium is >10.5 mg/dl. Serum phosphate is often low (<2.5 mg/dl).
- Hypercalciuria and hyperphosphaturia are often present.
- Alkaline phosphatase (ALP) is elevated due to high bone turnover.
- Elevated serum levels of PTH confirm the diagnosis of hyperparathyroidism.
- Preoperative sestamibi-iodine subtraction scanning and neck ultrasound are used to locate parathyroid adenomas. CT and MRI are usually not required unless carcinoma or ectopic parathyroids are suspected.
- Bone radiographs may show demineralization, subperiosteal resorption of bone (especially in the radial aspects of the fingers), mottling of the skull ("salt-and-pepper appearance"), or pathologic fractures. Articular cartilage calcification (chondrocalcinosis) is sometimes found.
- Dual energy X-ray absorptiometry (DEXA) may show reduced bone density.

Treatment

Parathyroidectomy

- Parathyroidectomy is recommended for patients with symptomatic hyperparathyroidism, kidney stones, bone disease, pregnancy and very high serum calcium. During pregnancy, parathyroidectomy is performed in the second trimester.
- Subtotal parathyroidectomy is indicated for parathyroid hyperplasia. Three and one-half glands are usually removed, and a metal clip is left to mark the location of residual parathyroid tissue.
- Parathyroid carcinoma is treated by en bloc resection of the tumor and the ipsilateral thyroid lobe. Adjuvant treatment includes radiation therapy.

Treatment of Hypercalcemia

Hydration

- With oral or IV fluids.

Bisphosphonates

- Bisphosphonates inhibit bone resorption and decrease serum calcium. Pamidronate 30 mg (in normal saline) or zoledronic acid 4 mg can be given as intravenous infusion. Calcium decreases over several days and the effect may last for weeks to months.

Calcimimetics

- Calcimimetic agents activate the calcium-sensing receptor in the parathyroid gland, thereby inhibiting PTH secretion. Cinacalcet is a calcimimetic agent. Cinacalcet may be administered orally in doses of 30–250 mg daily. It reduces serum calcium levels.

Estrogen-progestin therapy

- Estrogen-progestin therapy is beneficial in postmenopausal women with primary hyperparathyroidism because of its ability to reduce bone resorption.

Q. Enumerate the causes of hypercalcemia. Discuss the management of hypercalcemia.

Q. Hypercalcemic crisis.

- Normal calcium level in the body is 8–10 mg/dl. Out of this 4–5.6 mg/dl is ionized calcium and the remaining is bound to albumin. Hence, total calcium concentration may be high with high serum albumin and low with low albumin concentration. This can be corrected by using

the formula, Ca = Serum Ca + 0.8 × (Normal albumin – patient albumin).
- Calcium level of 10.5–12 mg/dl is mild hypercalcemia and level above 14 mg/dl indicates severe hypercalcemia.

Etiology of Hypercalcemia

Increased bone resorption
- Primary hyperparathyroidism
- Secondary and tertiary hyperparathyroidism
- Malignancy
- Thyrotoxicosis

Increased calcium absorption
- Increased calcium intake
- Chronic kidney disease
- Milk alkali syndrome
- Hypervitaminosis D

Miscellaneous causes
- Lithium
- Pheochromocytoma
- Adrenal insufficiency
- Rhabdomyolysis and acute renal failure
- Familial hypocalciuric hypercalcemia
- Immobilization

Clinical Features

Renal
- Polyuria
- Polydipsia
- Nephrolithiasis
- Nephrocalcinosis
- Distal renal tubular acidosis
- Nephrogenic diabetes insipidus
- Acute and chronic renal insufficiency

Gastrointestinal
- Nausea, vomiting
- Bowel hypomotility and constipation
- Pancreatitis
- Peptic ulcer disease

Musculoskeletal
- Muscle weakness
- Bone pain
- Osteopenia/osteoporosis

Neuropsychiatric
- Anxiety, depression
- Decreased concentration
- Confusion, stupor, coma

Cardiovascular
- Shortening of the QT interval
- Bradycardia
- Hypertension

Eye
- Calcium may precipitate in the corneas ("band keratopathy")

Hypercalcemic Crisis

- Often seen in elderly patients with primary hyperparathyroidism.
- Clinical features are dehydration, hypotension, abdominal pain, vomiting, and altered sensorium.

Investigations

- Serum calcium should be corrected for albumin, and an elevated concentration should be confirmed by repeat testing.
- ECG may show shortened QT interval, AV block, bundle branch block, and prolonged PR and QRS.
- Serum PTH level helps to distinguish PTH-mediated from non-PTH-mediated causes of hypercalcemia. In hyperparathyroidism PTH level is elevated.
- Serum concentration of PTH-related protein (PTHrp) is elevated in malignancy related hypercalcemia.
- Serum concentration of the vitamin D metabolites, 25-hydroxyvitamin D (calcidiol) and 1,25-dihydroxyvitamin D (calcitriol), should be measured if there is no obvious malignancy and neither PTH nor PTHrp levels are elevated.
- Serum uric acid and LDH are elevated in malignancy.
- Plasma protein electrophoresis, urine for Bence-Jones protein and bone marrow examination are useful to rule out multiple myeloma.
- Chest X-ray, ultrasound abdomen and CT scan to rule out malignancy.
- Bone scan to rule out bone metastases.

Management

Mild to Moderate Hypercalcemia

- Patients with mild hypercalcemia do not require immediate treatment. Factors which aggravate hypercalcemia should be avoided. These are drugs such as thiazide diuretics and lithium, volume depletion, prolonged bed rest, and high calcium diet (>1000 mg/day). Adequate hydration is recommended. Symptomatic patients are treated with biphosphonates.

Severe Hypercalcemia (Calcium >14 mg/dl; Hypercalcemic Crisis)

- Rehydration with isotonic saline at an initial rate of 200 to 300 ml/h that is then adjusted to maintain the urine output at 100 to 150 ml/h.
- Administration of salmon calcitonin 4 IU/kg initially and then every 6 to 12 hours.
- Bisphosphonates: Zoledronic acid (4 mg IV over 15 minutes) or pamidronate (60 to 90 mg over two hours).
- Steroids: Prednisolone 5–15 mg 6 hourly or hydrocortisone 100 mg 6 hourly IV. Steroids inhibit vit D conversion to calcitriol. They are helpful in vit D intoxication, malignancies and granulomatous diseases.
- Calcitonin plus saline reduces calcium concentration within 12 to 48 hours whereas bisphosphonates will be effective by the second to fourth day.

- Hemodialysis should be considered if serum calcium is above 18 mg/dl.

Treatment of the Underlying Cause

- Such as malignancy, hyperparathyroidism, etc.

Q. Hypoparathyroidism.

- Hypoparathyroidism is characterized by deficiency of PTH and hypocalcemia.

Causes

- Post-surgical.
- Autoimmune.
- Autosomal dominant hypoparathyroidism.
- Pseudohypoparathyroidism (resistance to PTH).

Clinical Features

- Features of hypocalcemia are seen (see under hypocalcemia).

Treatment

- In acute manifestations of hypocalcemia (such as tetany), intravenous calcium gluconate is given.
- Vitamin D supplementation—vitamin D (in the form of vitamin D_2, or ergocalciferol), or calcitriol (1,25-dihydroxyvitamin D) are give orally daily to maintain normal calcium levels.

Q. Discuss the etiology, clinical features, investigations and management of hypocalcemia.

Q. Enumerate the causes of tetany. Discuss the clinical features and management of tetany.

Q. Trousseau's sign; Chvostek's sign.

- Hypocalcemia is an abnormal reduction in serum ionized calcium concentration (<8.8 mg/dl). Only ionized, free serum calcium affects neuromuscular function and is clinically important.

Etiology of Hypocalcemia (Tetany)

Hypoparathyroidism
- After parathyroid, thyroid, or radical neck surgery
- Idiopathic
- Infiltration of the parathyroid gland
- Pseudohypoparathyroidism

Vitamin D deficiency
- Nutritional deficiency
- Intestinal malabsorption
- CKD
- Acute pancreatitis
- Vitamin D resistance

Miscellaneous
- Hyperphosphatemia
- Hypomagnesemia (can cause relative PTH deficiency and end-organ resistance to PTH action.
- Massive blood transfusion (citrate-anticoagulated blood can decrease the concentration of ionized Ca)
- Alkalosis (hyperventilation, excessive vomiting)
- Fluoride intoxication
- Septic shock (due to suppression of PTH release and decreased conversion of 25(OH)D to $1,25(OH)_2$ D)

Clinical Features

- *Neuromuscular manifestations (tetany):* Hypocalcemia leads to neuromuscular irritability leading to tetany. Tetany is uncommon unless the serum ionized calcium concentration falls below 4.3 mg/dl. Other factors that worsen tetany are alkalosis, hypomagnesemia, hypokalemia and serum epinephrine concentrations. Tetany is characterized by both sensory and motor features. Initially sensory symptoms such as circumoral numbness, paresthesias of the hands and feet are seen. Motor symptoms are stiffness and clumsiness, myalgia, and muscle spasms and cramps. Hand muscle spasm leads to adduction of the thumb, flexion of the metacarpophalangeal joints and wrists, and extension of the fingers. Spasm of the respiratory muscles and of the glottis can cause cyanosis. Autonomic manifestations include diaphoresis, bronchospasm, and biliary colic. Latent tetany may be present when signs of overt tetany are lacking. It can be demonstrated by Trousseau's and Chvostek's signs. *Trousseau sign* is the induction of carpal spasm by inflation of a sphygmomanometer above systolic blood pressure for three minutes. It can also be induced by hyperventilation for one to two minutes after release of the cuff. Trousseau's sign is due to the ischemia of the nerve trunk under the cuff which increases excitability. *Chvostek's sign* is contraction of the ipsilateral facial muscles when facial nerve is tapped anterior to the ear. This leads to contraction of corner of the mouth, the nose and the eye.
- Other neurological features are seizures (both focal and generalized), intellectual impairment, extrapyramidal disorders such as parkinsonism, dystonia, hemiballismus, and choreoathetosis.
- Psychiatric manifestations—emotional instability, anxiety, depression, confusion, hallucinations, and frank psychosis. All are reversible with treatment.

- Skin manifestations—dry skin, hyperpigmentation, dermatitis and eczema, and psoriasis. Hair is brittle and sparse with patchy alopecia.
- Eye—cataracts.
- Dental—dental abnormalities occur when hypocalcemia is present during early development. They include dental hypoplasia, failure of tooth eruption, defective enamel and root formation, and abraded carious teeth.
- Cardiovascular—hypotension (in acute hypocalcemia), decreased myocardial contractility, and congestive heart failure.
- Gastrointestinal—steatorrhea due to impaired pancreatic secretion, gastric achlorhydria.
- Skeletal—Hypocalcemia associated with hypophosphatemia, as in vitamin D deficiency, causes rickets in children and osteomalacia in adults.
- Endocrine manifestations—impaired insulin release.

Investigations

- Serum calcium level is low.
- Serum PTH level is low in hypoparathyroidism and elevated in secondary hyperparathyroidism.
- Serum vit D level is low in vit D deficiency.
- Serum magnesium level—hypomagnesemia causes hypocalcemia by inducing PTH resistance or deficiency. Serum magnesium should be measured in any patient with hypocalcemia in whom the cause is not clear.
- ECG shows prolonged QT interval.

Management

- Tetany can be treated by rebreathing expired air in a paper bag or administering 5% CO_2 in oxygen. This increases arterial carbon dioxide which increases ionized calcium.
- Injection of 20 ml of a 10% calcium gluconate slow IV raises the serum calcium concentration immediately. An intramuscular injection of 10 ml may be given to obtain a more prolonged effect.
- Intravenous magnesium is given to correct the hypocalcemia associated with hypomagnesemia.
- Persistent hypoparathyroidism and pseudohypoparathyroidism are treated with oral calcium salts and vitamin D.

Q. Give a brief account of hormones secreted by the adrenal gland and their functions. Enumerate the diseases caused by adrenal gland dysfunction.

- Adrenal gland consists of adrenal cortex and medulla. Adrenal cortex is futher divided into zona glomerulosa, zona fasciculata, and zona reticularis (remember GFR for glomerulosa, fasciculata and reticularis)
- Zona glomerulosa consists of small epithelioid cells which secrete aldosterone (mineralocorticoid).
- Zona fasciculata consists of polygonal columnar cells, which secrete cortisol (glucocorticoid).
- Zona reticularis consists of a network of interconnecting cells which secrete adrenal androgens (dehydroepiandrosterone (DHEA)).
- Adrenal medulla consists of chromaffin cells which secrete adrenergic hormones such as epinephrine, norepinephrine and dopamine.

Actions of Adrenal Gland Hormones

Mineralocorticoids (aldosterone)

- Helps maintain blood volume and blood pressure by retaining sodium and water.

Glucocorticoids (cortisol)

- Regulation of intermediary metabolism. They counter hypoglycemia, induce protein catabolism and enhance lipolysis. Glucocorticoids also affect the adaptive response to stress and inflammation, immunity, wound healing and muscle and myocardial integrity.

Adrenal androgens

- Required for the growth of axillary and pubic hair in both males and females.

Epinephrine (also known as adrenaline) and norepinephrine

- These 2 hormones prepare the body for the fight-or-flight response by increasing the heart rate, constricting blood vessels, increasing the metabolic rate, and increasing the respiratory rate.

Diseases Caused by Adrenal Dysfunction

Hyperfunctioning of adrenal gland

- Glucocorticoid excess—Cushing's syndrome
- Aldosterone excess—hyperaldosteronism (primary aldosteronism—Conn's syndrome, secondary aldosteronism)
- Androgen excess—virilization
- Adrenal medulla—pheochromocytoma

Hypofunctioning of adrenal gland

- Primary—due to inability of the adrenals to produce hormones (Addison's disease)
- Secondary—due to deficient ACTH secretion by pituitary
- Tertiary—due to deficient CRH production by hypothalamus

Q. Discuss the etiology, clinical features, investigations and management of Cushing's syndrome (glucocorticoid excess).

- Cushing's syndrome is due to chronic glucocorticoid excess. The most common cause is iatrogenic, due to prolonged administration of glucocorticoids such as prednisolone.

Etiology

ACTH-dependent Cushing's syndrome
- Pituitary adenoma secreting ACTH (i.e. Cushing's disease)
- Ectopic ACTH syndrome
- Ectopic CRH syndrome
- ACTH therapy

ACTH-independent Cushing syndrome
- Adrenal adenoma
- Adrenal carcinoma
- Micronodular hyperplasia
- Macronodular hyperplasia
- Steroid therapy

Pseudo-Cushing's syndrome (cortisol excess as part of another illness)
- Major depressive disorder
- Alcoholism
- Primary obesity

Clinical Features

- The typical patient with Cushing's syndrome is a middle-aged plethoric woman with truncal obesity and hypertension.
- Obesity—the obesity is central (centripetal obesity) with sparing of limbs which gives "lemon on stick appearance". There is accentuation of normal fat over the upper part of the back, giving a "buffalo hump" appearance. The neck is thick and short. The supraclavicular fat pads are enlarged.
- Skin manifestations—include skin atrophy, easy bruisability, and purple striae in the trunk, breasts, and abdomen. Fungal infections are common. In pituitary tumors secreting ACTH, and in ectopic ACTH syndrome, hyperpigmentation can occur.
- Menstrual irregularities—oligomenorrhea, amenorrhea, etc.
- Signs of adrenal androgen excess—women with Cushing's syndrome often have signs of androgen excess. These include hirsutism, thinning of scalp hair, deepening of voice, and clitoral enlargement.
- Proximal muscle wasting and weakness.
- Osteoporosis is common and may lead to pathologic fractures and vertebral collapse. Low back pain is a common presenting feature. Occasionally, patients can present with avascular necrosis of the femoral head. Increased resorption of bones can lead to hypercalciuria and renal calculi .
- Neuropsychiatric symptoms—emotional lability, depression, irritability, anxiety and panic attacks.
- Diabetes mellitus may develop due to increased hepatic gluconeogenesis and insulin resistance.
- Hypertension and cardiovascular risk is a major cause of morbidity and mortality.

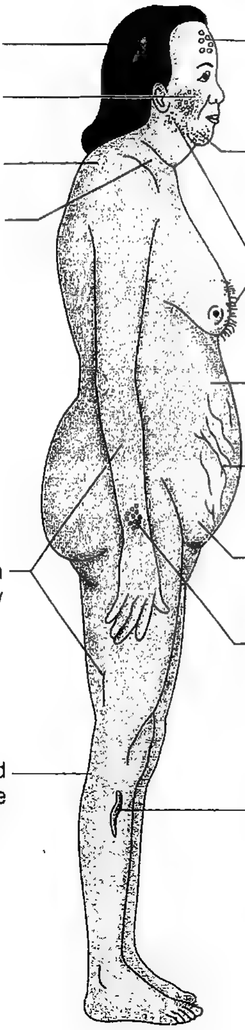

Fig. 9.3: Clinical features of Cushing's syndrome

Investigations

- Investigations are useful to confirm the diagnosis of Cushing's syndrome and to find out the etiology.

To Confirm the Presence of Cushing's Syndrome

- Serum cortisol level—serum cortisol level is normally lowest at 12 midnight. There is loss of diurnal variation in Cushing's syndrome, and midnight level is high. Recently, it has been shown that salivary cortisol concentration correlates well with blood level and can be used instead of blood level. In iatrogenic Cushing's syndrome, cortisol level is low unless the patient is taking a corticosteroid (such as prednisolone) which cross-reacts in immunoassays with cortisol.
- 24-hour urinary cortisol excretion is high in patients with Cushing's syndrome (normal <90 μg/24-hour). The patient can be assumed to have Cushing's syndrome if basal urinary cortisol excretion is more than three times the upper limit of normal.
- Overnight dexamethasone suppression test—1 mg of dexamethasone is given at 11 PM to 12 AM, and serum

cortisol is measured at 8 AM the next morning. In most normal patients, this drug suppresses morning serum cortisol to ≤1.8 µg/ml, whereas patients with Cushing's syndrome virtually always have a higher level.

- Low dose dexamethasone suppression test—this is an alternative to overnight dexamethasone suppression test. 0.5 mg dexamethasone is given 6th hourly for 2 days. 24-hour urine cortisol on second day and 8 AM serum cortisol after 48 hrs are measured. Urine cortisol <36 µg/day or serum cortisol <1.8 µg/dl excludes Cushing.

To Establish the Cause of Cushing's Syndrome

- Once the presence of Cushing's syndrome is confirmed, measurement of plasma ACTH is the key to establishing the differential diagnosis.
- Increased cortisol level and an undetectable ACTH indicates an adrenal pathology. Increased cortisol level with increased ACTH level indicates either pituitary source or an ectopic source of ACTH.
- Pituitary and ectopic source of ACTH can be differentiated by the fact that pituitary tumors, but not ectopic tumors, retain some features of normal regulation of ACTH secretion. Thus, pituitary ACTH secretion is suppressed by dexamethasone (although at a higher dose than normal) and ACTH secretion is increased by corticotropin-releasing hormone (CRH).
- MRI with gadolinium contrast enhancement can localize the tumors secreting ACTH or cortisol.
- Venous catheterization with measurement of inferior petrosal sinus ACTH (i.e. draining directly from the pituitary) may be helpful in confirming Cushing's disease if the MRI does not show a microadenoma of pituitary.
- CT or MRI detects most adrenal adenomas.

Additional Tests

- Serum electrolytes (usually high sodium and low potassium), glucose (elevated), glycosylated hemoglobin and bone mineral density measurement.

Management

- Most patients are treated surgically with medical therapy given for a few weeks prior to operation.

Medical Therapy

- Includes the following drugs:
  - *Somatostatin analogues*: Pasireotide is a somatostatin analogue that binds and activates human somatostatin receptors resulting in inhibition of ACTH secretion, which leads to decreased cortisol secretion. It is indicated for treatment of Cushing's disease in which pituitary surgery is not an option or has not been curative.
  - *Adrenal steroid inhibitors*: Metyrapone, ketoconazole, etomidate.
  - *Glucocorticoid receptor antagonist*: Mifepristone.
  - *Adrenolytic agents*: Mitotane. This drug causes adrenal cortical necrosis.

Surgery

- In Cushing's disease, trans-sphenoidal surgery with selective removal of the adenoma is the treatment of choice.
- Adrenal adenomas are removed via laparoscopy or a loin incision.
- Ectopic ACTH syndrome—localized tumors (e.g. bronchial carcinoid) should be removed. Unresectable malignancies may be treated by radiotherapy and chemotherapy. Medical therapy can be used for recurrences.

Q. Nelson's syndrome.

- This syndrome occurs in patients who have undergone bilateral adrenalectomy for Cushing's disease.
- Complete loss of negative feedback from adrenal glands leads to development of pituitary macroadenoma secreting ACTH.
- Clinical features include development of hyperpigmentation (due to high ACTH) within one or two years following adrenalectomy, headache and visual disturbances (due to pressure effect of macroadenoma). There may be signs of hypopituitarism due to compression of normal pituitary by the macroadenoma.
- Treatment involves resection of pituitary adenoma and irradiation.

Q. Discuss the etiology, clinical features, diagnosis, and management of mineralocorticoid excess (aldosteronism).

Or

Q. Discuss the etiology, clinical features, diagnosis, and management of primary hyperaldosteronism (Conn's syndrome).

Q. Secondary hyperaldosteronism.

- Hyperaldosteronism is the condition of excessive secretion of aldosterone from the adrenals. Primary hyperaldosteronism occurs due to excessive production of aldosterone within the adrenals. In secondary hyperaldosteronism the stimulus is extra-adrenal.
- Excessive production of aldosterone leads to hypertension, sodium retention, suppression of plasma renin and hypokalemia.

Etiology

Primary hyperaldosteronism
- Adrenal adenoma secreting aldosterone (Conn's syndrome)
- Idiopathic bilateral adrenal hyperplasia
- Glucocorticoid-suppressible hyperaldosteronism (rare)

Secondary hyperaldosteronism
- Pregnancy
- Inadequate renal perfusion, e.g. hypovolemia, cardiac failure, nephrotic syndrome, renal artery stenosis
- Renin-secreting renal tumor (very rare)

Clinical Features

- Sodium retention may cause edema and hypertension.
- Hypokalemia causes muscle weakness or even paralysis.
- Hypertension is common in primary aldosteronism and is due to sodium and fluid retention.
- Metabolic alkalosis—this is due to increased urinary hydrogen excretion mediated both by hypokalemia and by the direct stimulatory effect of aldosterone on distal acidification.

Investigations

- Serum electrolytes may show hypernatremia, hypokalemia and increased bicarbonate.
- Plasma renin activity and aldosterone levels—renin is low and aldosterone level is high in Conn's syndrome and bilateral adrenal hyperplasia.
- Abdominal CT is useful to detect any adrenal tumors.
- If CT is inconclusive, adrenal vein catheterization with measurement of aldosterone or ^{131}iodo-norcholesterol scanning may be helpful.

Management

Primary Hyperaldosteronism

- Aldosterone antagonists (spironolactone or eplerenone) can be used to treat both hypokalemia and hypertension in all forms of mineralocorticoid excess. High doses of spironolactone (up to 400 mg/day) may be required but cause gynecomastia.
- Amiloride (10–40 mg/day), which blocks the epithelial sodium channel regulated by aldosterone. or eplerenone can be used if spironolactone is not tolerated due to gynecomastia.
- Conn's adenoma is treated by unilateral adrenalectomy.
- Glucocorticoid-suppressible hyperaldosteronism is treated by suppression of ACTH, e.g. with dexamethasone.

Secondary Hyperaldosteronism

- Underlying cause should be treated.

Q. Pheochromocytoma.

- Pheochromocytoma is catecholamine-secreting tumor that arises from chromaffin cells of the adrenal medulla and the sympathetic ganglia. The catecholamines secreted include norepinephrine, epinephrine, and dopamine.
- 90% of tumors arise in adrenal medulla. There is a useful 'rule of tens' in this condition: 10% are malignant, 10% are extra-adrenal (i.e. in sympathetic ganglia), 10% are bilateral, and 10% are familial.
- Pheochromocytoma may be part of the syndrome of familial multiple endocrine neoplasia (MEN) types 2A and 2B, in which other endocrine tumors (parathyroid or medullary carcinoma of the thyroid) coexist or develop subsequently.

Clinical Features

- Paroxysmal hypertension associated with pallor (occasionally flushing), palpitations, sweating, headache and anxiety (fear of death). Classic triad is considered to be episodic headache, sweating, and tachycardia in association with hypertension.
- Abdominal pain, vomiting.
- Constipation.
- Weight loss.
- Glucose intolerance.

Investigations

- Plasma catecholamines (epinephrine, norepinephrine and dopamine) are increased.
- Plasma free metanephrine is elevated and is 99% sensitive. Since plasma metanephrine is continuously elevated, it is more sensitive than measurement of plasma catecholamines which are intermittently elevated during a paroxysm.
- Measurement of catecholamine metabolites (e.g. vanillylmandelic acid (VMA); conjugated metanephrine and normetanephrine) in 24 hours urine collection shows increase in excretion.
- CT or MRI of the abdomen can localize the tumor.
- MIBG scan—metaiodobenzylguanidine (MIBG) resembles norepinephrine and is taken up by adrenergic tissue. MIBG scan can detect tumors not detected by CT or MRI.
- Selective venous sampling with measurement of plasma norepinephrine can localize the tumor in difficult cases.

Management

- Surgical excision of the tumor is the treatment of choice. Preoperative preparation is done with α-blocker phenoxybenzamine or labetalol.

- If excision is not possible, medical therapy with alpha and beta blocking drugs (phenoxybenzamine and propranolol, or labetalol) is necessary. Beta blockers should not be given alone, as unopposed alpha action will lead to hypertensive crisis.

Q. Discuss the etiology, clinical features, investigations and management of adrenal insufficiency.

Q. Discuss the etiology, clinical features, investigations and management of Addison's disease.

- Adrenal insufficiency results from destruction or dysfunction of the entire adrenal cortex. It affects glucocorticoid and mineralocorticoid function.
- It is of two types: Primary (inability of the adrenals to produce hormones), secondary (due to pituitary or hypothalamic disease leading to ACTH and CRH deficiency). Primary adrenal insufficiency is also known as Addison's disease.
- Adrenal insufficiency can be acute or chronic. Acute adrenal insufficiency (acute adrenal crisis) is a medical emergency.

Etiology

Idiopathic
- Sporadic

Infections
- Tuberculosis
- HIV/AIDS
- Histoplasmosis

Carcinoma
- Metastatic carcinoma
- Lymphoma

Infiltrative diseases
- Hemochromatosis
- Sarcoidosis
- Amyloidosis

Iatrogenic
- Bilateral adrenalectomy
- Postradiotherapy

Adrenal hemorrhage
- Waterhouse-Friedrichsen syndrome following meningococcal septicemia
- Anticoagulation
- Trauma

Drugs
- Aminoglutethimide, metyrapone, ketoconazole

Genetic
- Congenital adrenal hyperplasia
- Polyglandular syndromes

Secondary (↓ACTH)
- Hypothalamic or pituitary disease
- Withdrawal of glucocorticoid therapy

Clinical Features

- Symptoms and signs are due to low glucocorticoid, low mineralocorticoid, low adrenal androgen levels and secondary increase in ACTH and renin.
- Glucocorticoid deficiency causes malaise, fatigue, generalized weakness, nausea, vomiting, anorexia, weight loss, postural hypotension with postural drop and hypoglycemia.
- Mineralocorticoid deficiency causes hyponatremia and hyperkalemia. Salt craving, may be present in some patients.
- ACTH excess in primary adrenal deficiency (Addison's disease) causes hyperpigmentation. Hyperpigmentation is seen in exposed areas or pressure sites such as knuckles, elbows, knees, palmar creases, nail beds, nipples, tongue, buccal mucosa, gums and conjunctivae. Hyperpigmentation is not seen in secondary adrenal insufficiency as ACTH is low. Vitiligo may be seen especially with autoimmune etiology.

Investigations

- Serum cortisol level—an early morning (between 8 and 9 AM) serum cortisol concentration less than 3 µg/dl suggests adrenal insufficiency and a value above 19 µg/dl excludes it.
- ACTH stimulation test (Synacthen test)—250 µg of ACTH (Synacthen) is given by IM injection at any time of day. Blood samples are drawn at 0 and 30 minutes for plasma cortisol. In normal subjects plasma cortisol is >17 µg/dl either at baseline or at 30 minutes. Cortisol levels fail to increase in primary adrenal insufficiency.
- Serum ACTH level—primary and secondary adrenal insufficiency can be distinguished by measurement of ACTH which is low in ACTH deficiency and high in Addison's disease.
- Serum electrolytes—hyponatremia and hyperkalemia are seen.
- HIV test if risk factors for infection are present.
- Plain X-ray abdomen may show adrenal calcification in tuberculosis.
- Ultrasound abdomen is useful to assess the size of adrenals and also to detect any tumors.
- CT or MRI of adrenals to look for size of adrenals and metastatic malignancy.
- Adrenal and other organ specific antibodies may be present in autoimmune adrenalitis.

Management

- Patients should receive lifelong steroid replacement therapy.
- Cortisol 15 mg in the morning and 5 mg at 6 PM or prednisolone 5 mg in the morning and 2.5 mg in the evening.
- During intercurrent illness the dose of steroid should be doubled. During surgery, oral stroid should be changed to parenteral dose, i.e. hydrocortisone 100 mg 6 hourly for 24 hours, then 50 mg IM 6 hourly until ready to take tablets.
- Patient should carry a steroid card all the time which should give information regarding diagnosis, steroid, dose and doctor. Patients should be encouraged to wear a bracelet engraved with the diagnosis all the time. All these can help in emergencies.
- Underlying cause should be treated.

Q. Acute adrenal crisis (acute adrenal insufficiency; Addisonian crisis).

Acute adrenal crisis can occur in the following situations:

- Serious infection or other major stress in a previously undiagnosed patient with adrenal insufficiency.
- Skipping of steroid or failure to increase the dose in a patient with known adrenal insufficiency during major illness or stress.
- Bilateral adrenal hemorrhage (Waterhouse-Friederichsen syndrome, anticoagulant therapy).
- Pituitary apoplexy.
- Rapid withdrawal of steroids in a patient who is taking them for a long time.

Clinical Features

- Hypotension or shock.
- Dehydration.
- Nausea, vomiting and abdominal pain. Abdominal rigidity or rebound tenderness may be present mimicking acute abdomen.
- Confusion or disorientation.
- Fever may be present due to underlying infection.
- There may be hyperkalemia, hyponatremia, hypoglycemia, lymphocytosis and eosinophilia.

Management

- It is a medical emergency.
- Rapid replacement of steroid, sodium and water deficits are the primary goals of therapy.
- IV fluid (DNS) is started immediately.
- In hydrocortisone 100–200 mg is given intravenously and repeated every 4–6 hours thereafter. 50 mg hydrocortisone can be given IM if there is problem with IV access.
- Once the patient's condition improves, he is put on oral steroids and oral fluids and the dose of steroids is slowly tapered to the maintenance dose.
- The precipitating cause should be identified and treated.

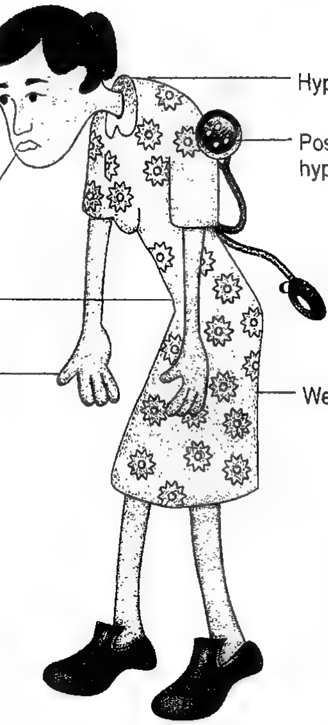

Fig. 9.4: Clinical features of adrenal insufficiency

Q. Waterhouse-Friderichsen syndrome.

- This refers to acute adrenal insufficiency due to bilateral adrenal hemorrhage.
- It is caused by severe infection with meningococcus or other bacteria. Rarely, it can be caused by adrenal vein thrombosis leading to venous stasis and hemorrhage.
- Clinical features are same as that of acute adrenal insufficiency. There is development of hypotension with shock. Patient may complain of abdominal pain especially in the flanks. There may be signs of meningococcal infection such as meningitis, cutaneous hemorrhages, etc. In the advanced stages, patient has respiratory failure and slips into coma.
- Treatment is same as that of acute adrenal insufficiency. In addition, appropriate antibiotics should be used to treat meningococcal septicemia (penicillin G) or other bacterial sepsis.

Q. Steroid therapy.

- Steroids are among the most widely used class of drugs.

Equivalent Doses of Steroids

- Hydrocortisone: 20 mg
- Cortisone acetate: 25 mg
- Prednisolone: 5 mg
- Deflazacort: 6 mg
- Methyl prednisolone: 4 mg
- Dexamethasone: 0.5 mg

Indications for Steroids

- Adrenal insufficiency
- Anaphylaxis
- Bronchial asthma
- Cerebral edema
- Connective tissue diseases
- Autoimmune diseases
- Nephrotic and nephritic syndrome
- Septic shock
- ARDS
- Leukemia, lymphoma
- In malignancies along with chemotherapy
- TB pericarditis
- Demyelinating diseases
- TB meningitis

Contraindications for Steroids

- Active tuberculosis
- Peptic ulcer
- Uncontrolled diabetes
- Uncontrolled hypertension
- Active infection

Side-effects of Steroid Therapy

- Suppression of pituitary hypothalamic axis.
- Cushingoid features.
- Glucose intolerance or diabetes mellitus.
- Hypertension.
- Mood disturbance, either depression or mania and insomnia.
- Gastric erosions due to impaired prostaglandin synthesis.
- Latent tuberculosis may be reactivated.
- Osteoporosis
- Proximal myopathy.

Measures to Minimize Side Effects

- Give the minimum effective dose.
- Give on alternate day rather than daily.
- Give in the morning.
- Give for the minimum possible duration.
- Monitor blood sugar during therapy.
- H2 blockers or proton pump inhibitors to reduce gastric side effects.
- Calcium and vit D to prevent osteoporosis.

Withdrawal of Steroid Therapy

- Steroid therapy for more than 3 weeks can cause pituitary adrenal suppression, and if stopped suddenly may cause acute adrenal insufficiency (crisis). Hence, steroid withdrawal must be gradual. All patients must be advised to avoid sudden drug withdrawal.

Q. Congenital adrenal hyperplasia.

Etiology

- Congenital adrenal hyperplasia is due to defects in various enzymes in the cortisol biosynthetic pathway. 21-hydroxylase deficiency causes 90% of all cases of congenital adrenal hyperplasia.
- 21-hydroxylase deficiency causes defective conversion of adrenal precursors to cortisol and, in some cases, to aldosterone. Accumulated hormone precursors (such as 17-OH-progesterone) are shunted into androgen production, causing virilization.
- Cortisol deficiency results in impaired negative feedback and increased ACTH secretion. Increased ACTH causes adrenal hyperplasia and excess production of steroids 'proximal' to the enzyme block.
- All these enzyme defects are inherited as autosomal recessive traits.

Clinical Features

- Cortisol (glucocorticoid) deficiency causes weight loss, hypotension, fatigability, etc. Aldosterone deficiency leads to hyponatremia, hypovolemia and hyperkalemia. Androgen excess causes ambiguous genitalia in girls, precocious pseudopuberty, amenorrhea and/or hirsutism.
- 17-hydroxylase and 11β-hydroxylase deficiency may produce hypertension due to excess production of 11-deoxycorticosterone, a mineralocorticoid.

Investigations

- High level of plasma 17-OH-progesterone is found in 21-hydroxylase deficiency.
- ACTH level is elevated.
- Ultrasound or CT abdomen shows adrenal hyperplasia.
- In siblings of affected children, antenatal diagnosis can be made by amniocentesis or chorionic villus sampling.

Management

- The aim is to replace deficient corticosteroids, and also suppress ACTH and hence adrenal androgen production.
- This can be achieved by giving a large dose of a long-acting synthetic glucocorticoid such as prednisolone

before going to bed to suppress the early morning ACTH peak, and a smaller dose is given in the morning.
- If hirsutism is the main problem, anti-androgen therapy is given.

Q. Hirsutism.

- Hirsutism is the excessive growth of thick or dark hair in women in locations that are more typical of male hair growth patterns (e.g. mustache, beard, central chest, shoulders, lower abdomen, back, inner thigh). It is due to androgen excess due to many causes. Hypertrichosis is a separate condition. It is simply an increase in the amount of hair growth anywhere on the body.

Etiology

- Idiopathic
- Familial
- Polycystic ovary syndrome (PCOS)
- Congenital adrenal hyperplasia
- Ovarian and adrenal tumors
- Drugs (minoxidil, anabolic steroids, diazoxide)
- Acromegaly
- ACTH-induced Cushing's disease

Clinical Features

- Increase in hair is seen on the chin, upper lip, abdomen, and chest.
- Androgen excess also increases sebaceous gland activity, producing acne.
- Menstrual irregularities, anovulation, and amenorrhea are common.
- Defeminization (decrease in breast size, loss of feminine adipose tissue) and virilization (frontal balding, muscularity, clitoromegaly, and deepening of the voice) occur if androgen excess is severe.
- Hypertension is seen in Cushing's syndrome, adrenal 11-hydroxylase deficiency, or cortisol resistance syndrome.

Investigations

- Serum testosterone level is elevated.
- 17-hydroxyprogesterone level is elevated in congenital adrenal hyperplasia.
- Ultrasound abdomen to assess adrenals and ovaries.
- Adrenal CT.

Management

- Patients with mild hirsutism can be treated with an oral contraceptive.
- Postmenopausal women with severe hyperandrogenism should undergo laparoscopic bilateral oophorectomy to remove any hilar cell tumors if adrenals are normal.
- Girls with hyperandrogenism due to congenital adrenal hyperplasia may be treated with laparoscopic bilateral adrenalectomy.
- Any drugs causing hirsutism are stopped.
- Antiandrogen therapy—spironolactone, cyproterone acetate, finasteride, and flutamide have antiandrogenic activity and help to decrease hirsutism. These drugs should be used only in nonpregnant women.
- Local treatment—shaving, depilation, waxing, electrolysis, or bleaching are effective measures to remove excess hair. Eflornithine topical cream retards hair growth when applied twice daily to unwanted facial hair. Laser therapy is an effective treatment for facial hirsutism. Alopecia may be treated with minoxidil 2% solution applied twice daily to a dry scalp.

Q. Discuss the classification and pathogenesis of diabetes mellitus.

- Diabetes mellitus is a clinical syndrome characterized by impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia.
- Diabetes occurs worldwide and the incidence of both type 1 and type 2 diabetes is rising. Majority of diabetics have type 2 diabetes. Many factors such as greater longevity, obesity, unsatisfactory diet, sedentary lifestyle and increasing urbanization contribute to development of type 2 diabetes.
- The prevalence of diabetes varies considerably around the world, and is related to differences in genetic and environmental factors. Type 2 diabetes is now being observed in children and adolescents also.
- Type 1 diabetes was previously termed 'insulin-dependent diabetes mellitus' (IDDM) since it is associated with profound insulin deficiency requiring replacement therapy. Type 2 diabetes was previously termed 'noninsulin-dependent diabetes mellitus' (NIDDM) because patients retain the capacity to secrete some insulin but exhibit impaired sensitivity to insulin (insulin resistance) and can usually be treated without insulin replacement. However, in advanced type 2 diabetes there is profound insulin deficiency and it behaves like type 1 diabetes, requiring insulin.

Etiologic Classification of Diabetes Mellitus

I. Type 1 diabetes (beta cell destruction, leading to absolute insulin deficiency)
- Immune-mediated
- Idiopathic

II. Type 2 diabetes (associated with insulin resistance)

III. Gestational diabetes mellitus (GDM)

IV. Other specific types of diabetes

- Genetic defects of β cell function (earlier called MODY—maturity onset diabetes in the young)
- Genetic defects of insulin action
- Pancreatic disease (e.g. pancreatitis, trauma/ pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy)
- Endocrinopathies (acromegaly; Cushing syndrome; glucagonoma; pheochromocytoma; thyrotoxicosis)
- Drug-induced (e.g. corticosteroids, thiazide diuretics, diazoxide)
- Viral infections (e.g. congenital rubella, mumps, Coxsackie virus B)
- Uncommon forms of immune-mediated diabetes (stiff man" syndrome, anti-insulin receptor antibodies)
- Associated with genetic syndromes (e.g. Down syndrome; Klinefelter syndrome; Turner syndrome; DIDMOAD (Wolfram syndrome)—diabetes insipidus, diabetes mellitus, optic atrophy, nerve deafness; Friedreich's ataxia; myotonic dystrophy)

Normal Physiology

- In humans, blood glucose is maintained within a narrow range by a balance between factors which increase blood sugar and factors which decrease blood sugar. Factors which increase blood sugar are intestinal absorption of glucose after meals, gluconeogenesis and glycogenolysis by the liver. Factors which decrease blood sugar are glucose uptake by peripheral tissues, particularly skeletal muscles, glycolysis and glycogenesis.
- When blood glucose is high, there is stimulation of insulin secretion from pancreas which facilitates peripheral glucose uptake by liver and skeletal muscles.
- When intestinal glucose absorption declines between meals, hepatic glucose output (gluconeogenesis and glycogenolysis) is increased in response to low insulin levels and increased levels of the counter-regulatory hormones (glucagon and adrenaline).

Pathogenesis of Diabetes

Type 1 Diabetes

Genetic factors

- Genetic factors account for about one-third of the susceptibility to type-1 diabetes. The HLA haplotypes DR3 and DR4 are associated with increased susceptibility to type-1 diabetes in Caucasians.
- HLA-DQA1 and DQB1 code for proteins on the surface of cells which present foreign and self-antigens to T-lymphocytes. Defective presentation of autoantigens from beta cells may lead to autoimmunity and destruction of beta cells.

Autoimmunity

- Type 1 diabetes is a slowly progressive T cell-mediated autoimmune disease. Defective presentation of autoantigens derived from pancreatic islet β cells probably leads to the development of autoimmunity. The pathological picture in type 1 diabetes is characterized by 'insulitis'—that is, infiltration of the islets with mononuclear cells (macrophages, T-lymphocytes, natural killer cells and B-lymphocytes).
- Islet cell antibodies can be detected even before the clinical development of type 1 diabetes.
- Type 1 diabetes may be associated with other autoimmune disorders such as thyroid disease, celiac disease, Addison's disease, pernicious anemia and vitiligo.

Environmental factors

- Along with genetic factors, environmental factors are important for the expression of type 1 diabetes.
- Reduced exposure to microorganisms in early childhood limits maturation of the immune system and may increase susceptibility to autoimmune disease.
- Some viral infections (mumps, Coxsackie B4, retroviruses, rubella, CMV, EBV) may cause type 1 diabetes as evidenced by isolation of virus particles from the pancreas known to cause cytopathic or autoimmune damage to β cells.
- Dietary factors such as cow's milk, has been implicated in triggering type 1 diabetes. Children who are given cow's milk early in infancy are more likely to develop type 1 diabetes than those who are breastfed. Nitrosamines (found in smoked and cured meats) and coffee have also been proposed as potentially diabetogenic toxins.
- Stress may precipitate type 1 diabetes by increasing counter-regulatory hormones and immunomodulation.

Type 2 Diabetes

- In type 2 diabetes there is a combination of resistance to the action of insulin in liver and muscle, together with impaired pancreatic β cell function leading to 'relative' insulin deficiency. In the beginning there is increased insulin secretion to counteract insulin resistance. But as the disease progresses, there is progressive beta cell failure and insulin deficiency develops.

Insulin resistance

- Resistance to the action of insulin in the liver and muscle leads to overproduction and underutilization of glucose respectively leading to hyperglycemia. Type 2 diabetes is often associated with central (visceral) obesity, hypertension and dyslipidemia (elevated LDL cholesterol and triglycerides, low HDL cholesterol). Coexistence of this cluster of conditions is called 'insulin resistance

syndrome' or 'metabolic syndrome'. Metabolic syndrome predisposes to cardiovascular diseases.

- The exact cause of insulin resistance remains unclear. However, there are many factors which contribute to insulin resistance. Central obesity (especially intra-abdominal fat) causes insulin resistance because large quantities of free fatty acids (FFA) relased by adipose tissue compete with glucose to be utilized by peripheral tissues. Adipose tissue also releases many hormones (e.g. cortisol, adipokines) which may decrease the sensitivity of insulin receptors.
- Lack of exercise increases insulin resistance by down-regulation of insulin-sensitive kinases and by the accumulation of FFAs within skeletal muscle. Exercise allows noninsulin-dependent glucose uptake by muscles.

Pancreatic β cell failure

- There is progressive reduction in beta cell mass. There is deposition of amylin around beta cells which forms insoluble fibrils of amyloid leading to destruction of beta cells.

Genetic predisposition

- Genetic factors are important in the etiology of type 2 diabetes. There is almost 100%. Concordance rate in monozygotic twins. Many susceptibility genes have been found which increase the risk of developing diabetes.

Obesity

- Overeating increases the risk of type 2 diabetes, especially when combined with obesity and underactivity. The risk of developing type 2 diabetes increases tenfold in people with a body mass index of >30.

Aging

- Type 2 diabetes usually affects middle-aged and elderly. Most of them are over 50 years of age.

Other Specific Types of Diabetes

- Most of these types of diabetes have an obvious cause of destruction of pancreatic β cells. Endocrine diseases such as acromegaly or Cushing's syndrome cause diabetes by increasing counter-regulatory hormones.

Gestational Diabetes

- The term 'gestational diabetes' refers to hyperglycemia occurring for the first time during pregnancy. Many of these women ultimately develop permanent diabetes.
- During pregnancy, insulin sensitivity is reduced through the action of placental hormones and there is increased insulin demand. Beta cells may be unable to meet this demand which leads to development of gestational diabetes mellitus.

Q. Discuss the clinical features of diabetes mellitus.

Asymptomatic

- Many diabetics are asymptomatic and are detected during routine health check ups or when they are seen for some other illness. This is especially so in case of early type 2 diabetes.

Polyuria, Nocturia

- Occurs because of glucose in the urine which acts as an osmotic diuretic.

Polyphagia

- Though there is hyperglycemia, it cannot be used by cells due to lack of insulin or insulin resistance. Hence, a diabetic feels more hungry than usual.

Thirst, Dry Mouth

- This happens because high blood glucose absorbs water from the tissues causing dehydration and thirst. Polyuria also leads to dehydration and increased thirst.

Easy Fatigability

- Inability to properly utilize blood glucose leads to easy fatigability.

Delayed Wound Healing

- Hyperglycemia inhibits inflammatory response, chemotaxis, decreased neutrophil function, etc. which lead to delayed wound healing.

Weight Loss

- Since there is loss of calories in the form of glucose in the urine, there is negative energy balance and weight loss. A person loses weight in spite of eating more.

Symptoms of Peripheral Neuropathy

- Such as burning, tingling and numbness occur due to diabetic peripheral neuropathy. Initially these symptoms are felt in feet. Later on it may involve the legs and hands.

Blurring of Vision

- This is due to the change in refractory power of lens due to hyperglycemia. Diabetic retinopathy is also an other cause in advanced diabetes.

Recurrent Infections

- Uncontrolled diabetes is associated with an increased susceptibility to infection. Patients may present with skin sepsis (boils) and genital candidiasis, and complain of pruritus vulvae or balanitis.

Presenting as DKA and HHS

- Some patients present for the first time with one of the acute complications of diabetes such as diabetic ketoacidosis (DKA) or HHS (hyperglycemic hyperosmolar syndrome). DKA is common in type 1 diabetes and HHS in type 2 diabetes.

Other Features

- Nausea; headache
- Mood change, irritability, difficulty in concentrating, apathy
- Specific causes of diabetes may produce their own features.
- Most of the type 2 diabetics are overweight. Hypertension is present in at least 50% of patients with type 2 diabetes. Signs of hyperlipidemia such as xanthelasma and xanthomas may be present.

Comparative Features of Type 1 and Type 2 Diabetes (*Table 9.1*)

Q. Discuss the diagnosis of diabetes mellitus.

Q. Glucose tolerance test.

Q. Impared glucose tolerance (IGT).

Q. Impaired fasting glucose (IFG).

- Testing to detect type 2 diabetes and prediabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2) and have one or more additional risk factors for diabetes such as physical inactivity, first-degree relative with diabetes, high-risk race/ethnicity (e.g. African American, Latino, Native American, Asian American, Pacific Islander), women who delivered a baby weighing >9 lb or were diagnosed with GDM, hypertension, HDL cholesterol level <35 mg/dl and/or a triglyceride level >250 mg/dl, women with polycystic ovarian syndrome, IGT or IFG on previous testing, other clinical conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans), and history of CVD.
- In those without these risk factors, testing should begin at age of 45 years.
- If tests are normal, repeat testing at least at 3-year intervals is reasonable.

The American Diabetes Association (ADA) Criteria for the Diagnosis of Diabetes

A hemoglobin A1c (HbA1c) level of 6.5% or higher.

or

A fasting plasma glucose (FPG) level of 126 mg/dl or higher; fasting is defined as no caloric intake for at least 8 hours,

or

A 2-hour plasma glucose level of 200 mg/dl or higher during a 75-g oral glucose tolerance test (OGTT),

or

A random plasma glucose of 200 mg/dl or higher in a patient with classic symptoms of hyperglycemia (i.e. polyuria, polydipsia, polyphagia, weight loss) or hyperglycemic crisis

Table 9.1 Comparative features of type 1 and type 2 diabetes

	Type 1	Type 2
Prevalence	Uncommon (5–10% of diabetes cases)	Common (>80% of diabetes cases)
Typical age at onset	<40 years	>40 years
Duration of symptoms	Weeks	Months to years
Body weight	Normal or low	Obese
Ketoacidosis	Yes	Rarely
Rapid death without treatment with insulin	Yes	No
Autoantibodies	Yes	No
Diabetic complications at diagnosis	No	25% (because of late presentation)
Family history of diabetes	Uncommon	Common
Other autoimmune diseases	Common	Uncommon
HLA-DR3/4	Association	No association
Insulin secretion	Absent/severely decreased	Increased/decreased
Insulin resistance	Absent	Present
Acanthosis nigricans	No	Common

- Urine glucose tests should never be used alone to diagnose diabetes, since an altered renal threshold for glucose can produce similar findings.

Oral Glucose Tolerance Test (OGTT)

- OGTT is not recommended for routine clinical use but may be required in the evaluation of patients with IFG (impaired fasting glucose) or when diabetes is still suspected despite normal FBS. It is commonly done in the diagnosis of gestational diabetes mellitus.
- OGTT should be performed under controlled conditions to ensure its accuracy. The following should be ensured before doing OGTT.
  - 3 days of unrestricted diet (>150 g carbohydrates/day) and physical activity.
  - Patient should remain seated and not smoke during the test.
  - OGTT should be done after an overnight fast, using a glucose load containing 75 g of anhydrous glucose dissolved in water; 2 hr post load glucose levels of 200 mg/dl or greater establish the diagnosis of diabetes.
- Factors that decrease the value of OGTT include:
  - Carbohydrate restriction (<150 g for 3 days)
  - Bed rest or severe inactivity
  - Medical or surgical stress
  - Drugs (e.g. thiazides, steroids, β blockers, phenytoin)
  - Smoking
  - Anxiety from repeated needle sticks.
- Hence, OGTT should not be performed in acutely ill patients.

Interpretation of OGTT Results

	FBS (mg/dl)	Two hours PPBS (mg/dl)
Normal	<100	<140
IFG	100–125	Normal (<140)
IGT	Normal (<100)	140–199
Diabetes	≥126	≥200 mg/dl

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)

- 2-hour post load glucose 140–199 mg/dl with FBS being normal is called impaired glucose tolerance (IGT).
- FBS between 100 and 125 mg/dl with PPBS being normal is called impaired fasting glucose (IFG).
- Both IGT and IFG are now called 'pre-diabetes' states. People with these pre-diabetic states have a relatively high risk of developing diabetes and subsequent vascular disease. All patients with IFG and IGT should be treated with diet and exercise and should be followed up yearly for the progression to diabetes.
- Because individuals with IFG may exhibit severe post-prandial hyperglycemia, a 75-g OGTT should be performed in all these patients to rule out diabetes. If 2-hr post load glucose concentration is 200 mg/dl or more, it confirms diabetes; if between 140 and 199 mg/dl they are defined as having IGT.
- Individuals with HbA1c of 5.7–6.4% are also at increased risk of developing diabetes later and should be counseled about weight reduction (if overweight), diet control and exercise.

Q. Discuss the investigations done in a case of diabetes mellitus.

Q. Glycated hemoglobin (HbA1c).

- The investigations done in case of a diabetes mellitus are as follows:
  - Urinalysis
  - FBS/PPBS
  - OGTT
  - Glycated hemoglobin
  - Fasting lipid profile (FLP)
  - Renal function tests (urea, creatinine)
  - Other tests as required

Urinalysis

- Glucosuria occurs when blood sugar goes more than 180 mg/dl (renal threshold for glucosuria). Glucosuria can be detected by Benedicts test or glucose strips.
- Proteinuria can occur due to development of diabetic nephropathy. Urine should be tested in all diabetics for the presence of proteinuria which can be treated with ACE inhibitors.
- Ketone bodies may be present in DKA.

OGTT

- See above.

Glycated Hemoglobin (HbA1c)

- RBCs are freely permeable to glucose. As a result, glucose becomes irreversibly attached to hemoglobin (HbA1c) at a rate dependent upon the prevailing blood glucose. Since HbA1c circulates within RBCs whose lifespan lasts up to 120 days, its concentration reflects the average blood glucose level in the preceding 120 days (i.e. 3 months).
- Its normal concentration is 4–6%. It is abnormally elevated in diabetic persons with chronic hyperglycemia.

- It should be measured every 3 to 4 month intervals so that adjustments in therapy can be made to optimize diabetes control.
- The accuracy of HbA1c values can be affected by hemoglobin variants or derivatives; the effect depends on the specific hemoglobin variant or derivative and the specific assay used. Any condition that shortens RBC survival or decreases mean RBC age (e.g. recovery from acute blood loss, hemolytic anemia) will falsely lower HbA1c. Vitamins C and E are reported to falsely lower test results possibly by inhibiting glycation of hemoglobin.

Lipid Profile

- Obese patients with diabetes may have abnormal lipid profile characterized by high triglyceride, high LDL and low HDL cholesterol. High LDL is atherogenic and may contribute to macrovascular complications of diabetes.

Renal Function Tests

- Advanced diabetes is associated with diabetic nephropathy which may progress to renal failure. If renal failure develops urea and creatinine will be elevated.

Q. Discuss the management of diabetes.

Q. Medical nutrition therapy (MNT) of diabetes.

Q. Oral hypoglycemic agents (oral antidiabetic agents).

- Methods available for the treatment of diabetes are as follows:
  1. Diet and exercise
  2. Oral anti-diabetic drugs
  3. Insulin
  4. Pancreas or islet cell transplantation
- Early type 2 diabetes can be controlled by diet and lifestyle modification alone. Other patients will require drugs or insulin or both.

Goals of Diabetes Management

- To allow the patient to lead a completely normal life.
- To achieve a normal metabolic state.
- To prevent long-term complications of diabetes.

Diet and Exercise

Diet (Medical Nutrition Therapy)

- A well-balanced, nutritious diet is important in the management of diabetes.
- The components of the diet should be as follows.
  - Carbohydrates: 45–65% of total daily calories
  - Protein: 10–35%
  - Fat: 25–35% (of which saturated fat is less than 7%)
- High protein intake may cause progression of renal disease in patients with diabetic nephropathy; for these individuals, protein intake should be restricted to 0.8 gm/kg/day.
- Dietary fiber such as cellulose, gum, and pectin are indigestible by humans. Dietary fiber increases intestinal transit and has beneficial effects on colonic function. It slows glucose absorption rate so that hyperglycemia is slightly diminished. Fiber has a favorable effect on blood cholesterol levels also. Diabetics should consume fiber rich foods such as oatmeal, cereals, and beans.
- Artificial and other sweeteners such as aspartame, saccharin, and sucralose can be used instead of sugar by diabetics. They are well tolerated and do not increase blood sugar.
- Patients should avoid sweets and other high calorie foods, reduce fats and oils and increase the intake of green leafy vegetables. Obese patients should consume fewer calories to reduce their weight. Vegetarian food is encouraged and non-vegetarian food is discouraged in diabetics as non-vegetarian food can contribute significantly in terms of calorie and fat content.
- Patients should reduce alcohol consumption and stop smoking.

Exercise

- Regular exercise and healthy diet alone is enough for many patients with early type 2 diabetes. Regular exercise improves glycemic control and reduces insulin resistance. Exercise facilitates noninsulin dependent glucose entry into the cells.

Oral Anti-diabetic Drugs

- Oral drugs are mainly effective in type 2 diabetes because most of them stimulate endogenous insulin secretion which is absent in type 1 diabetes.
- The following are the groups of drugs available to treat diabetes mellitus.

- Sulfonylureas
- Biguanides
- Thiazolidinediones (TZDs)
- Alpha-glucosidase inhibitors
- Meglitinide derivatives
- Glucagon-like peptide-1 (GLP-1) agonists
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Selective sodium-glucose transporter-2 (SGLT-2) inhibitors
- Amylinomimetics
- Insulins

Sulphonylureas

Examples

- *First generation:* Tolbutamide, chlorpropamide
- *Second generation:* Glibenclamide, gliclazide, glipizide, glimepiride.
- Individual sulphonylureas differ in their potency, duration of action and cost. Tolbutamide and chlorpropamide are rarely used due to the availability of 2nd generation sulphonylureas. Chlorpropamide has longest duration of action (half-life 36 hours) and can cause prolonged hypoglycemia. Of the second-generation sulphonylureas, glibenclamide can cause severe hypoglycemia and should be avoided in the elderly. Gliclazide and glipizide cause a few side-effects but are short-acting. Glimepiride is long-acting, can be given once daily and has less chances of causing hypoglycemia.
- People with type 2 diabetes who fail to respond to initial treatment with sulphonylureas are considered 'primary treatment failures'.
- After many years of diabetes, beta cell function gradually worsens. When beta cells are completely exhausted, insulin secretion stops and sulphonylureas will not act. This is called 'secondary failure' (i.e. after a period of satisfactory glycemic control). With continuing follow-up, 'secondary failure' affects 3–10% of patients each year.

Mechanism of Action

- Sulphonylureas stimulate the release of insulin from the pancreatic β cell (insulin secretagogue). They act through a sulphonylurea receptor which is linked to a K^+ channel on the β cell surface. K^+ transport triggers insulin secretion.

Indications

- These are used in type 2 diabetes after a trial of diet and exercise fails to control blood sugar. Sulfonylureas are not effective in type 1 diabetes since these drugs require functioning beta cells to produce their effect on blood glucose.

Contraindications

- Severe hepatic or renal impairment.

Side Effects

- Hypoglycemia
- Chlorpropamide can cause flushing (disulfiram like reaction) and hyponatremia if given with alcohol.
- Idiosyncratic reactions: Skin rashes, leukopenia, and thrombocytopenia.

Biguanides

Examples

- Metformin is the only biguanide available. Phenformin has been withdrawn due to high incidence of lactic acidosis.

Mechanism of Action

- It increases insulin sensitivity and peripheral glucose uptake.
- It also impairs glucose absorption by the gut and inhibits hepatic gluconeogenesis.
- It does not stimulate insulin secretion and hence does not cause hypoglycemia.

Indications

- It is not associated with weight gain and hence preferred in obese type 2 diabetes patients.
- It can also be used in type 1 obese diabetic patients as they also have insulin resistance.
- Starting dose is 500 mg BD, can be increased to a maximum of 1 g TID.

Side Effects

- Lactic acidosis.
- GI intolerance.

Contraindications

- Impaired renal or liver function, severe shock, cardiac failure, peripheral vascular disease. In all these cases, there is tissue hypoxemia (hence, already there is acidosis) which can precipitate lactic acidosis.

Thiazolidinediones (Glitazones)

Examples

- Pioglitazone, rosiglitazone

Mechanism of Action

- They stimulate peroxisome proliferator-activated receptor-γ (PPAR-γ). These receptors are present mainly in adipose tissue and enhance the action of insulin. They also release adipokines such as adiponectin and resistin which alter insulin sensitivity in the liver. They do not stimulate insulin secretion and hence, hypoglycemia is not a problem.

Indications

- Usually given along with sulphonylureas in patients intolerant of metformin, or added with both sulphonylurea and metformin.

Side Effects

- Increase in body weight.
- Hepatotoxicity—troglitazone has been withdrawn because of hepatotoxicity and newer thiazolidinediones should be avoided in patients with liver dysfunction.
- Sodium and fluid retention, hence, must be avoided in cardiac failure.
- Increased risk of bladder has been found in with pioglitazone.

Alpha-glucosidase Inhibitors

Examples

- Acarbose, voglibose, miglitol

Mechanism of Action

- They inhibit alpha-glucosidase enzyme in the intestine which prevents formation of glucose and hence, absorption of glucose. They should be taken with each meal. They only lower post-prandial blood glucose. They can be combined with a sulphonylurea.

Side Effects

- Since unabsorbed glucose is fermented by intestinal bacteria with production of gas, patient complaints of flatulence and abdominal bloating. Unabsorbed glucose acts as an osmotic laxative and produces diarrhea.

Meglitinides and Amino Acid Derivatives

Examples

- Repaglinide, nateglinide.

Mechanism of Action

- These drugs are called prandial glucose regulators. These drugs directly stimulate endogenous insulin secretion (similar to sulphonylureas) and are taken immediately before food. Duration of action is less than sulphonylureas and hence, hypoglycemia is also less.

Side Effects

- Weight gain.

Glucagon Like Peptide-1 Agonists (GLP-1 Agonists)

Examples

- Exenatide, liraglutide, albiglutide, dulaglutide.

Mechanism of Action

- Incretins are gut hormones which potentiate glucose-induced insulin secretion. Glucagon-like peptide (GLP-1) is an incretin hormone which stimulates insulin secretion. In addition, GLP-1 suppresses glucagon secretion, delays gastric emptying, reduces appetite and encourages weight loss. GLP-1 is degraded by the enzyme, dipeptidyl peptidase-4 (DPP-4).
- GLP-1 analogues mimic GLP-1 action and can be used to treat type 2 diabetes. All these drugs are administered as subcutaneous injection like insulin.

Side Effects

- The main side effect is nausea and vomiting. Other side effects are diarrhea and headache.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Examples

- Sitagliptin, saxagliptin, linagliptin.

Mechanism of Action

- DPP-4 inhibitors prolong the action of incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) by degrading DPP-4. DPP-4 inhibitors can be used as a monotherapy or in combination with metformin or a TZD. They are given once daily and are weight neutral.

Side Effects

- The main side effect of DPP-4 inhibitors is nasopharyngitis or upper respiratory tract infection.
- Pancreatitis is another important side effect.

Selective Sodium-glucose Transporter-2 (SGLT-2) Inhibitors

- These are relatively new class of drugs approved recently.
- Examples are canagliflozin, dapagliflozin and empagliflozin.

Mechanism of Action

- SGLT-2 inhibitors lower the renal glucose threshold. Lowering the renal glucose threshold results in increased urinary glucose excretion thus reducing blood glucose values.

Side Effects

- Constipation, diarrhea, nausea, increased urinary frequency (osmotic diuresis due to glucosuria) and genitourinary infections (due to glucosuria).

Amylinomimetics

- Pramlintide acetate is an amylin analogue that mimics the effects of endogenous amylin, which is secreted by pancreatic beta cells. This agent slows gastric emptying, supresses glucagon, and regulate appetite.

Combination of Oral Agents

- Combining different oral drugs is more effective than either drug used alone. If the blood sugar is not under

control with either metformin or sulphonylurea, both can be combined. If blood sugar is still not under control, a glitazone can be added. Finally alpha-glucosidase inhibitors and incretin mimics can be added.

- If blood sugar is still uncontrolled with a combination of all the drugs, then insulin can be added to the oral drugs.

Insulin

- Patients, whose sugar remains uncontrolled even after using a combination of all the oral drugs and newer drugs require insulin.
- Oral drugs can be continued and insulin is added to oral drugs.
- Initially a single dose of intermediate-or long-acting insulin can be started at bedtime. Later on twice daily mixed insulin (short-acting plus intermediate-acting), or basal bolus type of insulin therapy (short-acting insulin before every meal and long-acting insulin as basal insulin) may be used.

Pancreas or Islet Cell Transplantation

- Both these procedures require suitable donors and long-term immunosuppression.
- Pancreas transplantation at the time of renal transplantation is becoming more widely accepted. Solitary pancreatic transplantation in the absence of a need for renal transplantation should be considered only in those patients who fail all other methods of treatment.
- Islet cell transplantation is a minimally invasive procedure, and easier than pancreas transplantation.

Q. Classify insulin preparations.

Q. Write briefly about different insulin preparations.

Q. Insulin analogues.

Q. Complications of insulin therapy.

- Discovery of insulin was one of the greatest milestones in medicine. It was discovered in 1921 by Banting and Best and they tried this on a patient in 1922. They received Nobel prize in medicine for this remarkable discovery. The structure of insulin was subsequently fully worked out by Sanger in 1956.

Classification of Insulin Preparations

Short-acting
- Regular or plain insulin
- Insulin lispro
- Insulin aspart
- Insulin glulisine

Intermediate-acting
- NPH insulin (neutral protamine Hagedorn, also called isophane insulin)
- Lente insulin (insulin zinc suspension)

Long-acting
- Insulin glargine
- Insulin detemir

Time Action Profiles of Insulin Preparations

- Insulin is injected subcutaneously into the anterior abdominal wall, upper arms, outer thighs and buttocks. Accidental intramuscular injection can occur sometimes, but of no consequence except increased risk of hypoglycemia due to rapid absorption.
- Insulin is injected using a syringe with a fine needle (which can be reused several times). Now-a-days pen injectors with insulin in cartridge have become popular because they are more convenient and portable.
- Insulin can also be administered through insulin pumps which provide continuous subcutaneous or intravenous infusion of insulin. Insulin pumps can be worn on the body or implanted into the subcutaneous tissue.
- Insulin is given intravenously while treating acute complications of diabetes such as DKA and HHS.

Indications for Insulin

- Type 1 diabetes
- Diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS).

Table 9.2 Time action profiles of insulin preparations

Insulin preparation	Onset of action	Peak action	Duration of action
Aspart/lispro/glulisine	<15 min	1–3 hours	3–5 hours
Regular (plain)	30 min	2–4 hours	5–8 hours
NPH/lente	2–4 hours	4–12 hours	10–18 hours
Glargine	2–4 hours	No peak	24 hours
Detemir	Slow	No peak at low doses. Higher doses may cause peak at 6–8 hours	Up to 24 hours

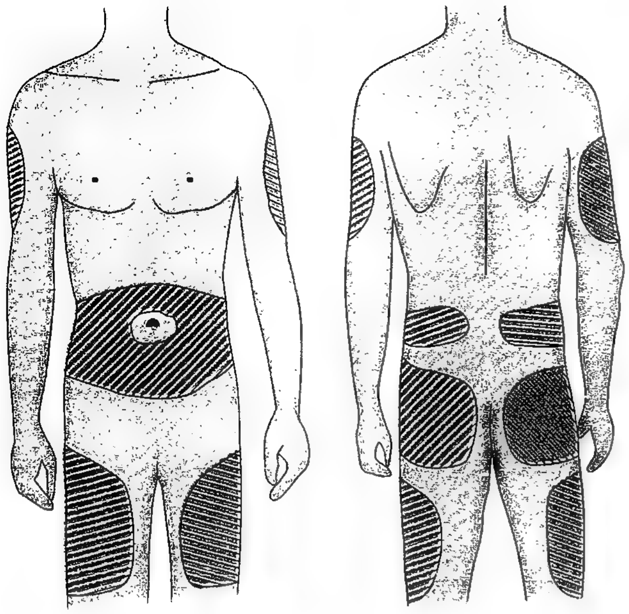

Fig. 9.5: Insulin injection sites

- Presence of serious infection or concurrent illness (e.g. acute M1, pancreatitis or stroke).
- Major surgery.
- Pregnancy—all pregnant women with diabetes mellitus, (whether gestational or previous diabetes) whose disease is not controlled with diet alone should be treated with insulin. All oral agents are contraindicated during pregnancy except metformin which is relatively safe.
- Symptomatic (polydypsia, polyuria, polyphagia and wt loss) uncontrolled diabetes, with persistent elevations of the FBS levels of 300 mg/dl or higher. Intensive insulin therapy with tight glycemic control helps reverse glucose toxicity. Therapy improves both insulin sensitivity and insulin secretion. After 6–8 wks of good glycemic control, these patients can be switched to an oral agent or can continue insulin therapy.

Insulin Regimens

- Various insulin regimens are used in the treatment of diabetes. Most people require two or more injections of insulin daily. Twice-daily administration of a mixture of short-acting and intermediate-acting insulin, given before breakfast and dinner is the commonly used regimen. Many pre-mixed insulin preparations are available containing different proportions of short-acting and intermediate-acting insulin (30:70 and 50:50).
- Multiple injection regimens require short-acting insulin before each meal, and a long-acting insulin injected at bedtime (basal-bolus regimen).

Regular Insulin or Plain Insulin

- Regular insulin is the natural insulin obtained from animal source or humans. There are only minor differences between human, pork and beef insulins. Animal insulins are more immunogenic than human insulin. Now-a-days the use of animal insulin has almost stopped due to the wide availability of recombinant human insulin.

	A Chain		B Chain
Species	**8th AA**	**10th AA**	**30th AA**
Human	Threonine	Isoleucine	Threonine
Pork (porcine)	Threonine	Isoleucine	Alanine
Beef (bovine)	Alanine	Valine	Alanine

- Regular insulin has an onset of action in 15–60 minutes after injection, a peak effect 2–4 hrs after injection and duration of action of 5–8 hrs.
- Regular insulin has to be injected 20–30 minutes before the meal.

NPH and Lente Insulin

- These two are intermediate-acting insulins.
- NPH (neutral protamine Hagedorn) insulin is produced by complexing regular insulin with protamine, a protein of fish origin and adding trace amounts of zinc. The protamine insulin complex is poorly soluble at physiologic pH and thus slowly absorbed from the subcutaneous tissue. Hagedorn is the name of the scientist who first formulated this preparation.
- Lente insulin is produced by adding zinc to regular insulin which prolongs its action. It dissolves slowly in body fluids and thus exhibits a prolonged duration of action after subcutaneous injection.

Insulin Analogues

- Insulin analogues are molecules that differ from human insulin in amino acid sequence but bind to same insulin receptors and function similarly as human insulin. They overcome some of the limitations of conventional insulin preparations.
- *Short-acting analogues:* Lispro, aspart, glulisine.
- *Long-acting analogues:* Glargine, detemir.

Insulin Lispro

- Insulin lispro was introduced in 1996. Lispro insulin is produced by interchanging two amino acids on beta chain i.e. proline at B-28, and lysine at B-29. The first three letters of lysine and proline were combined to name it as LYSPRO. Subsequently LYSPRO was changed to LISPRO since it was planned to release this all over the world and some languages do not contain the letter "Y". Lispro insulin is at least twice as fast acting as regular human insulin.

- After subcutaneous administration lispro begins acting within 15 mins, peaks in activity in 60 to 90 minutes and has a duration of action of 4–5 hrs.
- Because of its fast onset of action, lispro can be given within 15 minutes before meals. It can also be given immediately before or after meals. After taking injection, there is no need to wait for 30 mins to take meals (unlike regular insulin), hence lispro is also called no wait insulin. Advantages of insulin lispro over regular (plain) insulin.
- Because of its more rapid onset and peak action, insulin lispro more effectively controls postprandial blood sugar at 1 and 2 hrs than regular insulin.
- Lispro is more effective in suppressing hepatic glucose output than regular insulin, because of higher concentrations attained in liver.
- The onset of action of lispro does not vary much with the site of injection as compared to regular insulin.
- Regular insulin has to be injected 20–30 minutes before a meal. However, this is not so with lispro insulin which can be injected 0–15 minutes before a meal in all the patients. Hence, it is called "no-wait" insulin. It can even be injected after the meal.
- Because of its shorter duration of action, insulin lispro results in less late post-prandial hypoglycemia than regular human insulin. Insulin lispro is superior to regular insulin in the reduction of post-prandial hyperglycemia.

Insulin Aspart

- This is a rapidly acting analogue which was introduced after lispro in 2001. In insulin aspart, neutral proline in B-28 position is replaced by the negatively charged aspartic acid resulting in reduced capacity for self-association and faster absorption.
- The time-action-profile of aspart is similar to insulin lispro. Its advantages are similar to insulin lispro.

Insulin Glulisine

- Insulin glulisine is a new rapidly acting analogue with a pharmacokinetic profile that is similar to those of insulin lispro and insulin aspart. Trials are being conducted with this molecule.

Insulin Glargine

- Insulin glargine is a long-acting human insulin analogue produced by recombinant-DNA technology. It was introduced in 2001. This is the first true basal insulin.
- It differs from human insulin in that glycine replaces asparagine at position 21 of the A-chain, and two arginines are added to the C-terminus of the B-chain. Because of these changes, glargine remains completely soluble in the acidic pH of the vial (pH 4) but precipitates in the neutral pH of subcutaneous tissue after injection. It is then slowly released from these precipitates, prolonging its duration of action without producing any peak. It can be given once a day which provides basal level of insulin throughout the day.
- It is suitable for initial insulin therapy in both type 1 and type 2 diabetes. It is safe for use in children and adolescents. However, data are not available about its use in pregnant women.
- Glargine solution is clear and slightly acidic (pH 4) and should not be mixed with any other insulin or solution as this could alter its time-action-profile.
- Injection site redness, pain, itching, hives, swelling or inflammation are the most common type of adverse events, probably due to acidic pH of the solution.

Advantages

- Better control of FBS and decreased incidence of nocturnal hypoglycemia compared to NPH insulin.
- There is also more improvement in HbA1c level than with NPH insulin.
- The site of injection does not alter the time-action-profile of insulin glargine.
- The time of the day at which insulin glargine is injected does not alter glycemic control.
- The plasma levels of insulin glargine do not fluctuate significantly, thus mimicking physiological basal insulin profile.

Disadvantages

- No other insulin can be mixed in the same syringe. It is more acidic (pH 4.0) than other insulins (pH 7.4). If **insulin glargine** is mixed with another insulin, both lose activity.
- When using **insulin glargine,** three or more injections per day of a short-acting insulin may be needed before meals.
- Because it is clear, care must be taken not to confuse it with the short-acting insulin.
- It is also expensive.

Insulin Detemir

- Detemir is another new long-acting insulin analogue. Here, the amino acid threonine at B-30 position on the human insulin chain is lacking and a 14-carbon fatty acid (tetradecanoic acid or myristic acid) is attached to lysine at B-29.
- It is a clear solution with a neutral pH. It has a high affinity for serum albumin from which it gets released slowly which accounts for its unique mechanism of prolonged duration of action.

- Insulin detemir acts for nearly 24 hours. Detemir also has prominent action on hepatic glucose output which may be an advantage not seen with other insulins.

Advantages

- Absorption and action of insulin detemir is more predictable, because it is a clear solution and does not require resuspension and it does not precipitate after subcutaneous injection.

Complications of Insulin Therapy

Metabolic
- Hypoglycemia
- Weight gain
- Insulin edema

Local
- Lipoatrophy
- Lipohypertrophy
- Local allergic reactions

Systemic
- Immune insulin resistance
- Anaphylaxis

Q. Enumerate the complications of diabetes. What are the factors associated with increased mortality and morbidity in people with diabetes?

Acute complications
- Diabetic ketoacidosis (DKA)
- Hyperosmolar hyperglycemic state (HHS)
- Hypoglycemia
- Lactic acidosis

Chronic (long-term) complications

Microvascular
- Diabetic retinopathy
- Diabetic neuropathy
- Diabetic nephropathy

Macrovascular
- Coronary artery disease
- Peripheral vascular disease
- Cerebrovascular disease

Others
- Gastrointestinal (gastroparesis, diarrhea)
- Genitourinary (uropathy/sexual dysfunction)
- Dermatological
- Infections
- Cataracts
- Glaucoma
- Periodontal disease

Factors Associated with Increased Mortality and Morbidity in People with Diabetes

- Long duration of diabetes
- Early age at onset of disease
- Uncontrolled blood sugars (as evidenced by high HbA1c)
- Associated hypertension
- Proteinuria; microalbuminuria
- Dyslipidemia (high LDL, low HDL)
- Obesity

Q. Discuss the pathogenesis, clinical features, investigations, management and complications of diabetic ketoacidosis (DKA).

- Diabetic ketoacidosis (DKA) is a major medical emergency and remains a serious cause of morbidity and mortality in people with diabetes. It is more likely to occur in type 1 diabetes because of complete dependence on insulin.
- Many undiagnosed diabetics may present for the first time with DKA.

Pathogenesis of DKA

- DKA usually evolves rapidly, over a 24-hour period.
- The cardinal biochemical features of diabetic ketoacidosis are: Hyperglycemia, hyperketonemia and metabolic acidosis.
- Two hormonal abnormalities are largely responsible for the development of hyperglycemia and ketoacidosis in patients with uncontrolled diabetes; insulin deficiency and glucagon excess. However, DKA can develop even without glucagon excess. In addition to these factors, increased catecholamines and cortisol can contribute to the increase in glucose and ketoacid production.
- Hyperglycemia causes osmotic diuresis leading to dehydration and electrolyte loss, particularly of sodium and potassium. Average loss of fluid in DKA is 3–6 liters. Half the deficit is from intracellular compartment leading to cellular dehydration. Remaining half is derived from extracellular fluid compartment which leads to hemoconcentration, hypovolemia, hypotension, decreased renal perfusion and oliguria.
- Ketosis results from insulin deficiency, exacerbated by elevated catecholamines and other stress hormones, resulting in unrestrained lipolysis and supply of free fatty acids for hepatic ketogenesis. Excess accumulation of acidic ketones (β-hydroxybutyric acid and acetoacetate) leads to metabolic acidosis. Metabolic acidosis forces hydrogen ions into the cells, displacing potassium ions, which may be lost in urine or through vomiting leading to hypokalemia.
- There are many precipitating factors which may trigger an attack of DKA due to increased insulin requirements.

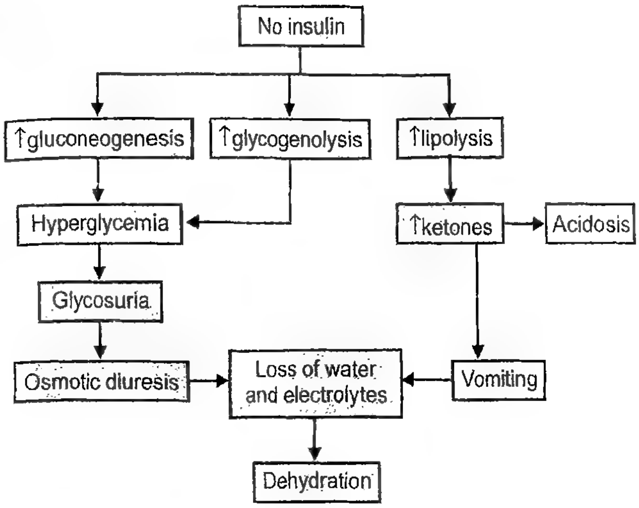

Fig. 9.6: Pathogenesis of DKA

Precipitating Factors for DKA

- Inadequate insulin treatment or noncompliance
- Infections (pneumonia, UTI, sepsis, etc.)
- Cerebrovascular accidents
- Myocardial infarction
- Acute pancreatitis
- Drugs (steroids, thiazides, clozapine or olanzapine, cocaine)

Clinical Features

Due to Hyperglycemia

- Polyuria, polydipsia, and weight loss are the initial symptoms. As hyperglycemia worsens, serum osmolality increases leading to neurological signs and symptoms such as lethargy, focal deficits and obtundation which can progress to coma. Blurred vision may occur due to change in the refractory power of lens due to hyperglycemia.

Due to Dehydration

- Loss of skin turgor, dry tongue, cracked lips, sunken eyeballs, tachycardia, and hypotension.
- Cold extremities, peripheral cyanosis.

Due to Metabolic Acidosis

- Deep and sighing breathing (Kussmaul breathing). Breath is usually fetid, and acetone smell may be present.
- Nausea, vomiting, and abdominal pain are common in DKA which may be related to acidosis. Abdominal pain is probably due to delayed gastric emptying and ileus induced by metabolic acidosis and electrolyte abnormalities.

Other Features

- Signs of underlying precipitating illness may be present such as fever in infections, signs of consolidation in pneumonia, etc.

Investigations

- Urea and creatinine—may be elevated due to severe dehydration.
- Electrolytes—sodium level is variable depending on the hydration status. Potassium and bicarbonate are usually low.
- Blood glucose is often >250 mg/dl.
- Serum amylase and lipase are elevated in DKA. Sometimes acute pancreatitis can precipitate an attack of DKA in which case amylase and lipase are elevated.
- Arterial blood gas (ABG) shows presence of metabolic acidosis.
- Plasma ketone bodies are raised.
- Urinalysis shows presence of sugar and ketone bodies.
- ECG may show changes due to electrolyte abnormalities or MI which might have precipitated DKA.
- Infection screen: Full blood count, blood and urine culture, C-reactive protein, chest X-ray.

Diagnostic Criteria for DKA

- Blood glucose >250 mg/dl
- Arterial pH <7.3
- Serum bicarbonate <15 mEq/L
- Moderate degree of ketonemia and/or ketonuria

Management of DKA

Principles of Treatment

- Correction of dehydration, hyperglycemia and electrolyte imbalance.
- Identification and treatment of precipitating events.
- Frequent patient monitoring.

Quick Initial Assessment

- Check airway and breathing first, especially in patients with altered sensorium. Take focused history and do brief physical examination. Send investigations. Patients with severe DKA require admission in the intensive care unit.

Fluid Replacement

- The average fluid loss is 3 to 6 liters in DKA. Initially 1 to 2 liters of isotonic saline is given rapidly intravenously. Subsequent rate of fluid replacement depends on the hydration status and urine output. Patients who are able to drink can take some or all of their fluid replacement orally.
- Fluid replacement also contributes to correction of hyperglycemia.

Correction of Hyperglycemia

- Unless the episode of DKA is mild, intravenous insulin infusion is the treatment of choice. Initially an

intravenous bolus of regular insulin at 0.15 units/kg body weight is given, followed by a continuous infusion at a dose of 0.1 unit/kg/hr (5 to 7 units/hr in adults).

- Blood glucose should be monitored every hour. It should fall by 50–75 mg/dl per hour. If plasma glucose does not fall by 50 mg/dl from the initial value in the 1st hour, check hydration status; if necessary, the insulin infusion may be doubled every 2-hour until a steady glucose decline between 50 and 75 mg/hr is achieved.
- When the blood glucose reaches 250 mg/dl, it may be possible to decrease the insulin infusion rate to 0.05–0.1 unit/kg/hr (3–6 units/hr), and dextrose (5%) may be started. Dextrose needs to be started along with insulin to facilitate continuation of insulin till the ketone bodies are cleared. This is because ketone bodies take longer time to clear than hyperglycemia.
- During therapy for DKA, blood should be drawn every 2–4 hr for determination of serum electrolytes, glucose and ketone bodies.
- Criteria for resolution of DKA includes a glucose <200 mg/dl, serum bicarbonate ≥18 mEq/L, and a venous pH of >7.3. Typical duration of therapy of DKA is usually 48 hours.

Potassium Replacement

- **If K** is <3.3 mEq, give 40 mEq/hour of K (2/3 as KCl, 1/3 as KPO_4) till K rises to ≥3.3
- **If K** is, ≥3.3 but less than 5 mEq, give 20–30 mEq of KCl/L in IV fluids (2/3 as KCl, 1/3 as KPO_4). Keep checking K hourly. Maintain between 4 and 5 mEq/L
- **If K** is ≥5 mEq, do not give any K. Monitor hourly.

Bicarbonate Replacement

- **If pH is <6.9,** give $NaHCO_3$, 100 mmol diluted in 400 ml of distilled water as infusion. Repeat HCO_3 administration every hour until pH is >7.
- **If pH is 6.9–7,** give $NaHCO_3$, 50 mmol diluted in 200 ml of distilled water.
- **If pH is** >7, no need to give bicarbonate.

Treatment of the Precipitating Event

- Such as infection should be treated with antibiotics.

Complications of DKA

- Hypoglycemia due to overzealous insulin therapy
- Hypokalemia due to insulin and bicarbonate therapy
- Cerebral edema—rare but frequently fatal complication of DKA, most common in children. Cerebral edema most likely happens because of rapid decline in plasma osmolality with treatment. It is minimized by gradual replacement of sodium and water (maximal reduction in osmolality 3 mOsm/kg H_2O/hour).
- ARDS.
- Mucormycosis (combination of hyperglycemia and acidic pH facilitates fungus growth).
- Myocardial infarction.
- Vascular thrombosis due to dehydration and increased viscosity of blood.
- Disseminated intravascular coagulation (rare).
- Acute circulatory failure due to dehydration.

Q. Hyperosmolar hyperglycemic state (non-ketotic hyperosmolar syndrome).

- Hyperosmolar hyperglycemic state (HHS) is characterized by severe hyperglycemia, hyperosmolality and dehydration in the absence of significant ketosis.
- It is more common type 2 diabetes, in middle-aged and elderly.

Precipitating Factors

- These are same as for DKA.

Pathogenesis

- Pathogenesis is same as DKA. In DKA, there is complete or severe deficiency of insulin which leads to formation of ketone bodies and acidosis. However, in HHS, some amount of insulin is present which is enough to prvent fatty acid oxidation and formation of ketone bodies. Hence, in HHS, significant ketosis and acidosis is absent.
- Dehydration and hyperglycemia are more severe than DKA.

Clinical Features

- Onset may be insidious over a period of days or weeks, with weakness, polyuria, and polydipsia.
- Signs of volume depletion and dehydration are present.
- Acidotic breathing (Kussmaul respirations) is absent.
- Lethargy and confusion may be present which may progress to convulsions and deep coma.

Investigations

- Severe hyperglycemia is present (usually 600 mg/dl or more).
- Serum osmolality is markedly raised (>320 mOsm/kg).
- Ketosis and acidosis are usually absent or mild.
- Serum sodium may be low in mild dehydration due to urinary sodium losses. However, as dehydration progresses, serum sodium can exceed 140 mEq/L, contributing to increased serum osmolality.
- Urea and creatinine are usually elevated due to pre-renal azotemia.

Management

- Management of HHS is same as that of DKA with following changes.
- Fluid deficit is more in HHS (average of 6–10 liters) than DKA, hence more fluid is required. IV fluids should be changed to 5% dextrose with 0.45% saline when the blood glucose falls to 300 mg/dl. It is important to maintain serum glucose between 250 and 300 mg/dl till plasma osmolality is ≤315 mOsm/kg and patient is mentally alert.
- There is no role for bicarbonate therapy as pH is not affected in HHS.

Prognosis

- The overall mortality rate of HHS is more than ten times that of DKA. Prognosis is better when it is recognized early and prompt therapy is instituted.

Q. Enumerate the differences between DKA and HHS (see Table 9.3).

Q. Lactic acidosis.

- Lactic acidosis is the most common cause of metabolic acidosis in hospitalized patients. It is associated with elevated plasma lactate concentration above 4 mEq/L.

Causes of Lactic Acidosis

Type A lactic acidosis (associated with tissue hypoxia)
- Hypovolemia
- Cardiac failure
- Sepsis
- Cardiopulmonary arrest

Type B lactic acidosis (no tissue hypoxia)
- Biguanide therapy in type 2 diabetes with phenformin or metformin.
- Malignancy
- Alcoholism
- HIV infection

Clinical Features

- Nausea, vomiting.
- Presence of acidotic breathing (Kussmaul respirations).
- Altered sensorium ranging from stupor to coma.

Investigations

- Plasma bicarbonate and pH are markedly reduced (pH <7.2).
- Anion gap is increased.
- High lactic acid level (>4 mmol/L, normal is <2 mmol/L).

Treatment

- Intravenous sodium bicarbonate sufficient to raise the arterial pH to above 7.2, along with insulin and glucose.
- Despite energetic treatment, mortality rate is >50%. Sodium dichloroacetate may be given to lower blood lactate. Underlying cause should be treated.

Q. Define hypoglycemia. Discuss the causes, clinical features, diagnosis and management of hypoglycemia.

- Hypoglycemia is low plasma glucose level (<50 mg/dl) *plus* simultaneous hypoglycemic symptoms that reverse with dextrose administration.

Causes

- Missed, delayed or inadequate meal
- Intense exercise
- Alcohol
- Drugs: Sulphonylureas, insulin, quinine, pentamidine.
- Malabsorption, e.g. celiac disease

Table 9.3 Differences between DKA and HHS

Features	DKA	HHS
• **Common in**	Type 1 diabetes	Type 2 diabetes
• **Evolution**	Over hours	Over days or weeks
• **Alteration in sensorium**	Variable	Stupor/coma
• **Acetone smell in breath**	Present	Absent
• **Acidotic breathing (Kussmaul respirations)**	Present	Absent
• **Abdominal pain, vomiting**	May be present	Usually absent
• **Average fluid deficit**	3–6 liters	6–10 liters
• **Blood glucose**	>250	>600
• **Arterial pH**	<7.3	>7.3
• **Serum bicarbonate (mEq/L)**	<15	>5
• **Blood/urine ketones**	Positive	Absent or trace
• **Serum osmolality (mOsm/kg)**	Variable	>320
• **Mortality**	5–10%	20–30%

- Critical illness: Liver and renal failure, malaria
- Endocrine disorders; Addison's disease, insulinoma
- Malignancies: Sarcomas.
- Factitious (deliberately induced)
- Glycogen storage disorders
- Inborn errors of metabolism

Clinical Features

Autonomic symptoms (due to acute activation of the autonomic nervous system)
- Sweating
- Trembling
- Pounding heart
- Hunger
- Anxiety

Neuroglycopenic symptoms (due to glucose deprivation to the brain)
- Confusion
- Drowsiness
- Speech difficulty
- Inability to concentrate
- Incoordination
- Focal neurological deficits

Non-specific
- Nausea
- Tiredness
- Headache

- In most instances, patient can recognize the symptoms of hypoglycemia and take appropriate action which includes eating a snack or sugar, etc. However, in certain circumstances (e.g. during sleep, or when distracted by other activities) warning symptoms may not be perceived by the patient, so that appropriate action is not taken and neuroglycopenia with reduced consciousness occurs.
- In diabetic patients who are accustomed to high blood sugar, symptoms of hypoglycemia may occur at higher blood sugar levels. Similarly, patients who have experienced recurrent hypoglycemia attacks may not experience any symptoms even when the blood glucose is well below 50 mg/dl (hypoglycemia unawareness).

Complications of Severe Hypoglycemia

- Impaired cognitive function
- Intellectual decline
- Brain damage
- Coma
- Convulsions
- Transient ischemic attack, stroke
- Focal neurological lesions.
- Cardiac arrhythmias
- Myocardial ischemia
- Vitreous hemorrhage
- Hypothermia
- Accidents (including road traffic accidents) with injury

Measures to Prevent Hypoglycemia

- Do not skip meals after taking sulphonylurea or insulin.
- Use the correct dose of insulin and oral antidiabetic agents as prescribed.
- Avoid unaccustomed intense exercise especially on empty stomach.
- Take light snacks in between major meals and also at bedtime.
- Monitor blood sugar frequently.
- Carry supply of fast-acting carbohydrate (sweets, sugar, glucose tablets), and a glucagon injection while going for long travel.

Management of Hypoglycemia

- If the patient is conscious and able to swallow, glucose (50 g) or any other fast-acting source of carbohydrate (sweets, honey, etc.) can be given orally.
- If the patient is an altered sensorium and unable to swallow, intravenous glucose (50 ml of 50% dextrose) is given. Inj glucagon (1 mg by intramuscular injection) can also be given if IV access is a problem. As soon as the patient is able to swallow, glucose should be given orally.
- If hypoglycemia has occurred after the use of a long-acting insulin or drug such as glibenclamide, above treatment should be followed by an infusion of 10% dextrose for a few hours, to prevent recurrence of hypoglycemia.
- If the patient fails to regain consciousness after blood glucose is restored to normal, development of cerebral edema should be suspected. Cerebral edema has high mortality and morbidity, and should be treated with mannitol and high-dose oxygen.

Q. Somogyi phenomenon and dawn phenomenon.

Somogyi Phenomenon

- It is also known as post-hypoglycemic hyperglycemia. It refers to rebound hyperglycemia due to release of counter-regulatory hormones following an episode of hypoglycemia.
- It usually happens in the morning after an episode of hypoglycemia at midnight.
- Causes include excess or ill-timed insulin, missed meals or snacks and inadvertent insulin administration.
- It is important to recognize Somogyi phenomenon because control of morning hyperglycemia depends on decreasing the night dose of insulin instead of increasing it.

Diagnosing Somogyi Phenomenon

- Somogyi phenomenon should be suspected when morning hyperglycemia worsens or resists treatment with increasing insulin doses. Other clues are normal daytime blood sugar levels, and relatively low HbA1C. The most important thing in the diagnosis of Somogyi phenomenon is considering it in the causes of morning hyperglycemia.
- Documenting nocturnal (3–4 am) hypoglycemia confirms the diagnosis.

Managing Somogyi Phenomenon

- Reduce night or bedtime insulin.
- Giving night time intermediate-acting insulin (NPH/lente) at bed time rather than before dinner may help. Substitution of night dose NPH/lente with longer acting preparation (glargine, detemir) may also help. These measures will cause insulin effect to peak in the morning rather than at midnight.
- Substitution of regular insulin with a fast-acting insulin analogue, such as Lispro, may be of some help.
- Patient should be advised to take a bedtime snack to prevent midnight hypoglycemia.

Dawn Phenomenon

- It is due to early morning surge of growth hormone, which causes insulin resistance and early morning hyperglycemia.
- It can be differentiated from Somogyi phenomenon by documenting the absence of midnight hypoglycemia.
- It is managed by increasing the night dose of insulin.

Q. Discuss the risk factors, pathology, clinical features, diagnosis and management of diabetic nephropathy.

- Diabetic nephropathy is glomerular sclerosis and fibrosis caused by the metabolic and hemodynamic changes of diabetes mellitus. It manifests as slowly progressive albuminuria with worsening hypertension and renal insufficiency.
- Diabetic nephropathy is one of the most common causes of end-stage renal disease (ESRD). It is an important cause of morbidity and mortality.
- It is more common in type 1 than in type 2 diabetes.

Risk Factors for Developing Diabetic Nephropathy

- Genetic variables (decreased number of glomeruli)
- Family history of diabetic nephropathy
- Poor control of blood glucose
- Long duration of diabetes
- Ethnicity (e.g. Asian races, Pima Indians)
- Presence of hypertension
- Dyslipidemia
- Obesity
- Smoking

Pathology

- There are three major histologic changes in the glomeruli in diabetic nephropathy: Glomerular basement membrane thickening; mesangial proliferation; and glomerular sclerosis.
- The first change to be seen is glomerular basement membrane thickening which is associated with microalbuminuria. Subsequently, nodular deposits (the Kimmelstiel-Wilson lesion) develop, and glomerulosclerosis worsens (heavy proteinuria develops) until glomeruli are progressively lost and renal function deteriorates.
- Renal failure usually takes ≥10 years after the onset of nephropathy to develop.

Clinical Features

- Diabetic nephropathy can be asymptomatic or present with one of the following:
  - Passing of foamy urine.
  - Fatigue and foot edema secondary to hypoalbuminemia (if nephrotic range proteinuria is present).
  - In later stages, patients may develop symptoms and signs of uremia (e.g. nausea, vomiting, anorexia).
  - Hypertension is usually present.

Diagnosis

- Screening for microalbuminuria: Microalbuminuria is urinary excretion of albumin in a range of 30 to 300 mg albumin/day. Microalbuminuria can progress to macroalbunuria (excretion of >300 mg albumin per day) or nephrotic range proteinuria (>3 gm/day) over many years. All diabetic patients should be screened for albuminuria at the time of diagnosis and yearly thereafter.
- Quantification of albumin excretion can be done by the following methods:
  - Measurement of albumin-to-creatinine ratio on a spot urine test. A ratio of more than 30 mg albumin/g creatinine is abnormal.
  - 24-hour urine albumin excretion— >30 mg/24-hour is abnormal.
- *Renal function tests*—urea, creatinine may be elevated in advanced diabetic nephropathy.
- Ultrasound of kidneys is required to know the size of kidneys and any parenchymal changes.
- Kidney biopsy is not routinely necessary unless other kidney diseases are suspected such as glomerulonephritis, etc.

Management

- If there is evidence of nephropathy, further progression should be reduced by strict control of blood glucose and control of blood pressure.
- ACE inhibitors not only reduce blood pressure but also reduce proteinuria and progression of diabetic nephropathy. Angiotensin II receptor blockers (ARB) and non-dihydropyridine calcium antagonists (diltiazem, verapamil) also have similar benefits.
- Statins are used to treat dyslipidemia. They also reduce proteinuria.
- Renal replacement therapy (dialysis) is required in end-stage renal disease.

Q. Diabetic retinopathy.

- Diabetic retinopathy is one of the most common causes of blindness in adults.
- Diabetic retinopathy (DR) is divided into two major forms: Nonproliferative and proliferative, depending on the absence or presence of abnormal new blood vessels in the retina.

Pathogenesis

- The exact mechanism by which diabetes causes retinopathy is unknown. Many theories have been proposed. There are many mechanisms which can produce retinopathy such as: Increased production of sorbitol by polyol pathway, activation of protein kinase C (PKC), increased expression of growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1), hemodynamic changes, formation of advanced glycation end products (AGEs), oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS), and subclinical inflammation and capillary occlusion. Retinal capillary occlusion causes chronic retinal hypoxia and stimulates new vessel formation (neovascularization) and increases vascular permeability (causing retinal leakage and exudation).
- Nonproliferative retinopathy (also called background retinopathy) develops first and causes increased capillary permeability, microaneurysms, hemorrhages, exudates, macular ischemia, and macular edema.
- Proliferative retinopathy develops after nonproliferative retinopathy and is more severe. It is characterized by abnormal new vessel formation (neovascularization) which may rupture and cause retinal and vitreous hemorrhage. Neovascularization is often accompanied by preretinal fibrous tissue, which, along with the vitreous, can contract, resulting in traction retinal detachment.

Clinical Features

- Microaneurysms
- Retinal hemorrhages
- Exudates
- Cotton wool spots
- Venous changes
- Neovascularization
- Vitreous hemorrhage
- Fibrosis

Diagnosis

- Funduscopy
- Color fundus photography
- Fluorescein angiography
- Optical coherence tomography.

Management

- Severe non-proliferative and proliferative retinopathy is treated with retinal laser photocoagulation. Photocoagulation is used to destroy areas of retinal ischemia which stimulate neovascularization, to seal leaking microaneurysms and reduce macular edema, and to gliose new vessels directly on the retinal surface.
- Clinically significant macular edema is treated with intraocular injection of anti-VEGF drugs (e.g. ranibizumab, bevacizumab, aflibercept) and/or with focal laser photocoagulation.
- Vitrectomy may be used in selected cases where visual loss is due to recurrent vitreous hemorrhage which has failed to clear, or retinal detachment resulting from retinitis proliferans.

Prevention

- Good control of blood sugar and blood pressure.
- Regular screening for retinopathy at least once a year in all diabetic patients.

Q. Discuss the classification, pathology, clinical features, investigations and management of diabetic neuropathy.

Q. Autonomic neuropathy.

- Diabetic neuropathy is the most common complication of diabetes mellitus (DM), affecting as many as 50% of patients with type 1 and type 2 DM.
- It is asymptomatic in the majority, although it can cause disabling symptoms in a few patients. Its prevalence is higher with long duration of diabetes and poor control of blood sugar.

Classification

Symmetric polyneuropathy

Polyradiculopathies
- Lumbar polyradiculopathy (diabetic amyotrophy)
- Thoracic polyradiculopathy

Mononeuropathies
- Cranial mononeuropathy
- Peripheral mononeuropathy

Mononeuropathy multiplex

Autonomic neuropathy

Pathology

- Nerve damage is probably due to accumulation of advanced glycosylation end products and sorbitol and increased oxidative stress. The following changes are seen in nerve biopsy.
- Axonal degeneration of both myelinated and unmyelinated fibers.
- Thickening of Schwann cell basal lamina.
- Patchy, segmental demyelination.
- Thickened endoneural blood vessel walls and vascular occlusions.

Clinical Features

Symmetrical Polyneuropathy

- Distal symmetric sensorimotor polyneuropathy is the most common type of diabetic neuropathy. It is characterized by progressive loss of distal sensation, followed, in severe cases, by motor weakness.
- Symptoms include paresthesiae in the feet, and rarely, in the hands, pain in the lower limbs (dull, aching and/or lancinating, worse at night), burning sensations in the soles of the feet, cutaneous hyperesthesia and numbness in the feet.
- Examination shows loss of vibration sensation, altered proprioception distally and loss of tendon reflexes in the lower limbs. These features are due to large nerve fiber involvement. Impairment of pain, light touch and temperature is secondary to loss of small fibers.
- Muscle weakness and wasting develop only in advanced cases, but subclinical motor nerve dysfunction is common.
- All the above features start initially in the feet, but later as the disease advances, hands also get involved.

Polyradiculopathies

- *Lumbar polyradiculopathy (diabetic amyotrophy):* The most common type of diabetic polyradiculopathy is high lumbar radiculopathy involving the L2, L3, and L4 roots. Patient presents with thigh pain followed by painful proximal weakness and wasting in one leg. Tendon reflexes may be absent on the affected side(s). This condition is thought to be due to acute infarction of the involved nerve roots. Although recovery usually occurs within 12 months, some deficits become permanent. Management is mainly supportive.
- *Thoracic polyradiculopathy:* This is less common than lumbar polyradiculopathy and affects the T4 through T12 roots. Patient presents with abdominal pain, sometimes in a band-like pattern. Diagnosis is confirmed by EMG studies.

Mononeuropathies

- Mononeuropathies are usually severe and of rapid onset but eventually recover.
- Cranial mononeuropathy—cranial nerves 3, 4 and 6 are commonly affected. Patient presents with unilateral pain, ptosis, and diplopia, with sparing of pupillary function. Facial mononeuropathy (Bell's palsy) occurs more frequently in diabetic than in nondiabetics.
- Peripheral mononeuropathy—median, femoral and sciatic nerves are commonly involved. These are usually compression palsies. Median nerve gets compressed at the wrist commonly leading to carpal tunnel syndrome. Lateral popliteal nerve compression occasionally causes foot drop. Ulnar mononeuropathy, either at the elbow, or less commonly, at the wrist can also occur.

Mononeuropathy Multiplex

- Multiple mononeuropathies in the same patient are known as mononeuropathy multiplex (or asymmetric polyneuropathy).

Autonomic Neuropathy

- It can affect many organ systems, including cardiovascular, gastrointestinal, genitourinary, pupillary, sudomotor and neuroendocrine systems.
- Either parasympathetic or sympathetic nerves may be predominantly affected in one or more visceral system.

Manifestations of Autonomic Neuropathy

Cardiovascular
- Postural hypotension
- Resting tachycardia
- Fixed heart rate

Gastrointestinal
- Dysphagia, due to esophageal atony
- Gastroparesis (abdominal fullness, nausea and vomiting, delayed gastric emptying)
- Constipation, diarrhea, incontinence

Genitourinary
- Bladder dysfunction
- Erectile dysfunction and retrograde ejaculation

Sudomotor
- Gustatory sweating
- Anhidrosis; fissures in the feet

Vasomotor
- Feet feel cold, due to loss of skin vasomotor responses
- Dependent edema, due to loss of vasomotor tone and increased vascular permeability

Pupillary
- Decreased pupil size
- Resistance to mydriatics
- Delayed or absent reflexes to light

Investigations

- Simple clinical tests such as heart rate variation during deep breathing, heart rate response to standing and blood pressure response to standing.
- Baroreflex sensitivity using power spectral analysis of heart rate
- Nerve conduction studies.
- Assess glycemic control by FBS, PPBS and HbA1c.

Managemen

- Good control of diabetes.
- Pain control—neuropathic pain can be controlled by tricyclic antidepressants (amitriptyline), anticonvulsants (gabapentin, carbamazepine, phenytoin, pregabalin), topical capsaicin, opiates (tramadol, oxycodone) and duloxetine. Any one or more of these can be used.
- Autonomic neuropathy—postural hypotension can be reduced by full length elastic stockings, increasing salt intake, fludrocortisone and α-adrenoceptor agonist (midodrine). Gastroparesis may respond to prokinetic agents such as metoclopramide and domperidone. Diarrhea responds to diphenoxylate, loperamide and broad-spectrum antibiotics. Constipation can be managed by stimulant laxatives (senna). Bladder dysfunction can be managed by intermittent self-catheterization. Erectile dysfunction (impotence) by phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil).

Q. Diabetic foot.

- Foot complications are common in diabetics and if neglected can lead to amputation. Hence, foot care is very important in diabetics.

Etiology

- Both neuropathy and peripheral vascular disease play an important role in the causation of diabetic foot. Neuropathy promotes ulcer formation by decreasing pain sensation and perception of pressure. Peripheral vascular disease also contributes to ulcer formation and gangrene.
- Infection occurs as a secondary phenomenon following disruption of the protective epidermis.

Clinical Features

- *Due to neuropathy*—pain, paresthesiae and numbness, neuropathic ulcer.
- *Due to ischemia*—rest pain, cluadication, ischemic ulcer, gangrene.
- *Due to infection*—cellulitis, abscess, osteomyelitis and sepsis.

Management

- Good control of blood sugar.
- Removal of callus skin.
- Treatment of infection with appropriate antibiotics.
- Avoid weight-bearing on calluses and ulcers.
- Treatment of peripheral vascular disease.
- Amputation if there is extensive tissue necrosis, gangrene and/or bony destruction.
- Specially manufactured and fitted orthotic footware to prevent recurrence of ulceration and protect the feet of patients with Charcot neuroarthropathy.
- Use of foot wear made of microcellular rubber is helpful to prevent callus formation and ulcers.

Q. What is gestational diabetes mellitus? Discuss the pathophysiology, risk factors, diagnostic criteria, and management of gestational diabetes.

- Gestational diabetes mellitus (GDM) is defined as diabetes with first onset or recognition during pregnancy.
- Most GDM cases begin during pregnancy, but some GDM cases may be previously undetected type 1 or type 2 diabetes.

Pathophysiology

- Pregnancy is characterized by insulin resistance particularly during the second half of pregnancy which may predispose some women to develop diabetes.
- Insulin resistance is due to placental secretion of diabetogenic hormones such as growth hormone, cortisol, placental lactogen, and progesterone, as well as increased maternal adipose deposition, decreased exercise, and increased caloric intake.
- GDM develops when pancreas fails to compensate for increased insulin resistance.

Risk Factors for Gestational Diabetes

- Obesity
- Age greater than 25 years
- Ethnicity (South Asian, black, Hispanic, Native American)

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- Family history of diabetes.
- Previous glucose abnormalities in pregnancy.
- Previous macrosomia.

Diagnosis of GDM

Two-step Strategy

- **Step 1:** Perform a 50 g glucose tolerance test (nonfasting), with plasma glucose measurement at 1 hour, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. If the plasma glucose level measured 1 hour after the load is ≥140 mg/dl, proceed to a 100 g OGTT.
- **Step 2:** The 100 g OGTT should be performed when the patient is fasting.
- The diagnosis of GDM is made if at least two of the follwing four plasma glucose levels (measured fasting and 1 hours, 2 hours, 3 hours after the OGTT) are met or exceeded:

Fasting	95 mg/dl
1 hour	180 mg/dl
2 hours	155 mg/dl
3 hours	140 mg/dl

Significance of GDM (Effects on Mother and Fetus)

- Gestational diabetes is associated with an increased risk of later development of type 2 diabetes. Maternal morbidity is increased and there is a high chance of cesarean section. Pregnancy is also associated with an increased risk of ketoacidosis.
- Increased risk of perinatal mortality and morbidity for the baby. Maternal hyperglycemia stimulates fetal insulin production which stimulates fetal growth leading to macrosomia. Fetal macrosomia increases the risk of birth injury during delivery, and of subsequent neonatal hypoglycemia. There is also increased risk of polycythemia, hyperbilirubinemia and hypocalcemia in the fetus.

Management of GDM

- All women with GDM should receive nutritional counseling and nutrition therapy. Total calories should be distributed wisely throughout the day. Consumption of refined carbohydrates should be reduced. When nutritional therapy fails to maintain glucose at normal levels, insulin should be used.
- All the oral antidiabetic agents are contraindicated during pregnancy except metformin for polycystic ovarian syndrome (PCOS).
- Only human insulin should be used during pregnancy. 3–4 injections of short-acting insulin may be required to achieve good glucose control.
- Blood glucose should be monitored daily. Do not strive for normoglycaemia at the expense of hypoglycemia.

Q. Metabolic syndrome (insulin resistance syndrome (syndrome X).

- The co-occurrence of metabolic risk factors (abdominal obesity, hyperglycemia, dyslipidemia, and hypertension) is termed "metabolic syndrome". Patients with metabolic syndrome are at risk of developing type 2 diabetes and cardiovascular disease.
- Abdominal obesity increases the risk of metabolic syndrome. Excess abdominal fat leads to excess free fatty acids in the portal vein, increasing fat accumulation in the liver. Fat also accumulates in muscle cells leading to insulin resistance and hyperinsulinemia. Glucose metabolism is impaired, and dyslipidemia and hypertension develop. Serum uric acid level is usually elevated (increasing the risk of gout).
- Metabolic syndrome is diagnosed when any three of the following five traits are present:

- Abdominal obesity, defined as a waist circumference in men >40 inches and in women >35 inches.
- Serum triglycerides ≥150 mg/dl or drug treatment for elevated triglycerides.
- Serum HDL cholesterol <40 mg/dl in men and <50 mg/dl in women or drug treatment for low HDL-C.
- Blood pressure ≥130/85 mm Hg or drug treatment for elevated blood pressure.
- Fasting blood sugar ≥100 mg/dl or drug treatment for elevated blood glucose.

Clinical Implications

- The risk of following conditions is increased in people with metabolic syndrome:
  - Type 2 diabetes
  - Cardiovascular diseases
  - Fatty liver disease
  - Polycystic ovarian disease
  - Obstructive sleep apnea
  - Hyperuricemia and gout
  - Chronic kidney disease
  - Erectile dysfunction

Treatment

- Reduction of obesity is the main therapeutic goal. This can be achieved by regular exercise and low fat, high fiber diet. Pharmacologic therapy such as orlistat can be used for severe obesity.
- Control of hypertension, dyslipidemia and hyperglycemia by appropriate drugs. Metformin is used to treat insulin resistance.
- Cessation of smoking.

10 Diseases of Immune System, Connective Tissue and Joints

Q. What are the presenting complaints of musculoskeletal diseases?

- Joint pain
- Joint stiffness (subjective feeling of inability to move freely)
- Weakness
- Swelling
- Deformity (joint, bone)
- Systemic complaints (weight loss, loss of appetite, easy fatigability, etc.)

Q. What are the investigations done in musculoskeletal diseases?

- Plain X-rays.
- Synovial fluid analysis.
- Radionuclide bone scans (useful in detecting Paget's disease, and primary or secondary bone tumors).
- Bone mineral density (BMD) measurements: Useful to diagnose and quantify osteoporosis. Dual energy X-ray absorptiometry (DEXA) is the current method of choice.
- *CT and MRI*: Useful to assess anatomically complex structures, such as the spinal canal and facet joints.
- *Ultrasonography*: Useful in confirming soft tissue changes such as a hip joint effusion, popliteal cyst or thickened Achilles tendon.
- *Arthrography*: A contrast is injected and X-ray is taken. This is useful to demonstrate a ruptured popliteal ('Baker's') cyst.
- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR): These are acute phase reactants and elevated in infections and inflammation.
- *Autoantibodies*: Rheumatoid factor (RF), antinuclear antibodies (ANA), antiphospholipid antibodies and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Anti-CCP has more specificity for diagnosing rheumatoid arthritis than RF.
- Biochemical tests (calcium, phosphorus, uric acid, alkaline phosphatase).
- Bone biopsy.

Q. Enumerate the causes of monoarthritis.

- Monoarthritis refers to inflammation of only one joint.

Causes

- Septic arthritis
- Crystal induced arthritis (gout, pseudogout)
- Monoarticular presentation of oligo- or polyarthritis (reactive arthritis, psoriatic arthritis, rheumatoid arthritis, etc.)
- Trauma
- Hemarthrosis
- Foreign body reaction (e.g. plant thorn)
- Avascular necrosis
- Subchondral collapse or fracture

Q. Enumerate the causes of oligoarthritis.

- Oligoarthritis refers to arthritis affecting 2 to 4 joints.

Causes

- Osteoarthritis
- Seronegative spondyloarthropathies
- Reactive arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Enteropathic arthritis
- Erythema nodosum
- Juvenile idiopathic arthritis
- Oligoarticular presentation of polyarthritis
- Infections (bacterial endocarditis, neisseriae, mycobacteria).

Q. Enumerate the causes of polyarthritis.

- Polyarthritis refers to arthritis involving 5 or more joints.

Infections

- Gonococcal arthritis, rheumatic fever tuberculous arthritis, syphilitic arthritis, bacterial endocarditis, Lyme disease, viral arthritis.

(contd.)

Rheumatological diseases
- Rheumatoid arthritis, ankylosing spondylitis, SLE, systemic vasculitis, systemic sclerosis, polymyositis/dermatomyositis, Still's disease, Behçet's syndrome, sarcoidosis

Mechanical
- Degenerative joint disease—osteoarthritis

Malignancy
- Paraneoplastic arthropathies

Metabolic
- Hypothyroidism, hyperparathyroidism, Cushing's disease, hemochromatosis, Wilson's disease, ochronosis, hyperlipoproteinemias

Drug induced
- Hydralazine, procainamide (drug-induced lupus), thiazides (gout)

Q. Enumerate the causes of bone pain.

- Malignancy (primary or secondary bone tumors)
- Hematological malignancies such as myeloma and leukemia
- Fracture
- Paget's disease
- Osteoporosis
- Osteomalacia
- Chronic infection (osteomyelitis)
- Osteonecrosis

Q. Discuss the etiology, clinical features, investigations and management of osteoarthritis.

- Osteoarthritis (OA, osteoarthrosis) is the most common form of arthritis.
- It is characterized by damage to articular cartilage, new bone formation and remodelling of joint. Inflammation is not a prominent feature of OA.

Epidemiology

- The prevalence of osteoarthritis increases with aging. By 65 years of age, 80% of people have radiographic evidence of OA.
- It mainly affects weight bearing joints though certain small joints can also be involved. The knee and hip are most often involved.
- Knee OA is prevalent in all racial groups but hip, hand and generalized OA are only prevalent in Caucasians.
- OA is more common in females.

Etiology and Pathogenesis

- OA was previously thought to be a normal consequence of aging, thereby leading to the term degenerative joint disease. However, it is now realized that multiple factors play a role in the causation of OA.
- There are many risk factors for the development of OA which are as follows:
  - Advanced age
  - Female sex
  - Obesity
  - Occupation which involves repetitive loading of particular joints (e.g. shipyard workers)
  - Sports activities
  - Previous injury to joint
  - Muscle weakness
  - Proprioceptive deficits
  - Genetic factors
  - Acromegaly
  - Calcium crystal deposition disease

  - Many insults such as trauma, repetitive loading, metabolic, genetic or constitutional insults may damage a synovial joint and trigger the repair process.
  - The repair process involves new bone formation and remodeling of joint shape. New bone formation occurs at the margins of the joint called osteophytes. This may result in anatomically altered but pain-free functioning joint ('compensated' OA). However, poor repair process may result in progressive symptoms and joint failure.
  - Pathologically there is fissuring of the articular cartilage surface ('fibrillation'), development of deep vertical clefts, localized chondrocyte death and decrease in cartilage thickness. Decrease in the thickness of articular cartilage results in decrease in joint space. The bone immediately below the damaged articular cartilage develops cysts and there is increase in its trabecular thickness. The synovium also undergoes variable degrees of hyperplasia. These synovial changes may sometimes resemble those of rheumatoid arthritis.

Clinical Features

- The main symptoms of OA are pain and restriction of joint movement. Patient is usually above 45 years (often over 60 years).
- Pain is of insidious onset over months or years. Usually one or a few joints are affected and weight-bearing joints are commonly involved (such as knee and hip). It is variable or intermittent over time ('good days, bad days'). It is worse on movement and weight-bearing, and relieved by rest. Morning stiffness is less (<15 minutes) compare to rheumatoid arthritis (>1 hour).
- Examination of the involved joint shows restricted movement (due to capsular thickening and blocking by osteophyte), coarse crepitus on movement (due to rough articular surfaces), bony swelling (osteophyte) around joint margins, joint deformity, and joint-line tenderness.
- Muscle wasting is present around the involved joint.

- Generalized OA involves multiple joints. It initially starts at interphalangeal joints (IPJs) of fingers affecting distal interphalangeal joints (DIP) more than proximal interphalangeal joints (PIP). Affected joints develop posterolateral swellings on each side of the extensor tendon which enlarge and harden to become Heberden's (DIP) and Bouchard's (PIP) nodes.

Investigations

- Blood counts, ESR and CRP are normal.
- *Plain X-ray*: This shows reduced joint space, marginal osteophytes and joint deformities.
- *Synovial fluid analysis*: Predominantly viscous with low turbidity; calcium pyrophosphate crystals may be seen.

Management

Non-pharmacologic Therapy

- Short periods of rest during acute pain.
- *Reduction of risk factors*: Weight loss if obese, pacing of activities, use of a walking-stick for painful knee or hip OA, etc.
- Physiotherapy including muscle strengthening exercises.

Pharmacologic Therapy

- *Analgesics*: Paracetamol up to 4 g/day. Oral NSAIDs such as ibuprofen, diclofenac or aceclofenac, etc. can be used. Topical NSAIDs and capsaicin are also helpful in relieving the pain and inflammation.
- *Steroids*: Intra-articular injection of corticosteroid can be tried for severe pain.

Surgical Therapy

- Surgery is indicated if there is severe pain, progressive immobility and functional impairment in spite of conservative measures. Osteotomy (for malaligned joints), arthroscopic debridement, arthroplasty, joint replacement, etc. are options.

Q. Discuss the etiology, clinical features, investigations and management of rheumatoid arthritis.

- Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily involving joints. Its main feature is symmetric peripheral polyarthritis.
- RA occurs all over the world. Highest prevalence is in Pima Indians of Arizona and lowest in black Africans and Chinese. It is more common in females.

Etiology

- The exact cause of RA is unknown. It is thought to be an autoimmune disease.
- RA might be a manifestation of the response to an infectious agent in a genetically susceptible host. A number of infectious agents have been suspected which include Mycoplasma, Epstein-Barr virus (EBV), cytomegalovirus, parvovirus, and rubella virus.
- Evidence for genetic predisposition is suggested by higher incidence of RA in monozygotic twins than in dizygotic twins and increased frequency of disease in first-degree relatives of patients. Most patients with RA are HLA-DR4 positive.
- Female gender and cigarette smoking are risk factors for the development of RA.

Pathology

- RA is characterized by chronic inflammation, granuloma formation and joint destruction.
- The earliest change is swelling and congestion of the synovial membrane which becomes infiltrated with lymphocytes (CD4+ T cells), plasma cells and macrophages. These inflammatory cells release cytokines which stimulate the activation, proliferation and differentiation of B cells into antibody-producing plasma cells. These plasma cells produce antibodies against the Fc fragment of IgG which is termed as the rheumatoid factor.
- Inflammation of synovium leads to synovial hypertrophy and effusion of synovial fluid into the joint space leading to joint swelling. There is formation of inflammatory granulation tissue (pannus) which spreads over and under the articular cartilage, and damages it. Involved joint may develop fibrous or bony ankylosis.
- Muscles adjacent to inflamed joints atrophy and there may be focal infiltration with lymphocytes.
- Subcutaneous nodules consist of a central area of fibrinoid necrosis surrounded by radially arranged (palisade) mononuclear cells with strands of collagen.
- Rheumatoid vasculitis involves medium and small arteries and venules, with infiltration by lymphocytes.

Clinical Features

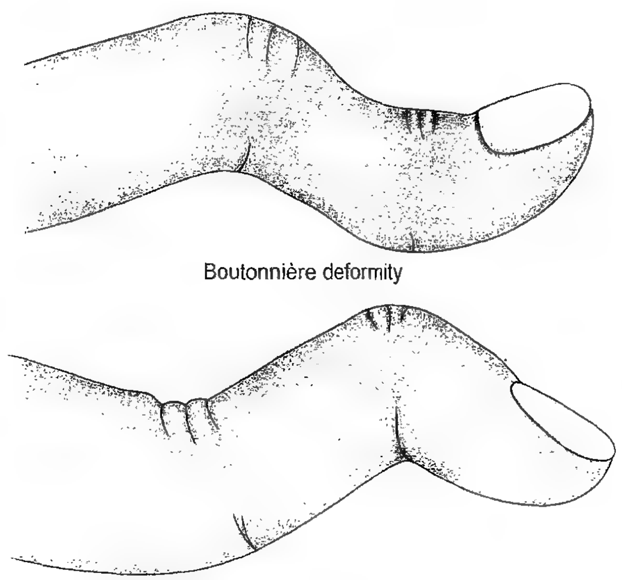
Articular Features

- RA is more common in females. The peak age of onset is in the fourth decade in females and slightly later in males.
- The onset can be monoarticular, oligoarticular or polyarticular.
- The most common presentation is insidious onset of symmetric polyarthritis. The joints involved are proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, shoulder, knee, ankle, and MTP joints. The distal interphalangeal (DIP) joints of the fingers are usually spared. Symmetrical joint involvement is common in middle-aged women.

- Acute onset with asymmetrical polyarthritis is more often seen in elderly patients.
- Asymmetrical presentation becomes symmetrical as the disease progresses.
- In the palindromic-onset type, joints are affected and resolve completely within hours to days and recur after a period of time. This type may finally evolve into classical symmetrical polyarticular pattern.
- Predominant symptoms are, stiffness, and swelling of involved joints.
- Morning stiffness is a common feature of RA and is defined as slowness or difficulty moving the joints when getting out of bed or after staying in one position too long. Stiffness usually lasts more than one hour.

Hands

- Swelling of the PIP joints with a fusiform or spindle-shaped appearance of the fingers. The DIP joints are usually spared (in osteoarthritis DIP joints are involved)
- Bilateral and symmetrical swelling of the MCP joints. Ulnar deviation of the fingers at the MCP joints.
- Swan-neck deformities due to extension of the PIP joints and flexion of the DIP joints. Boutonnière deformities due to flexion of the PIP joints and extension of the DIP joints.



Boutonnière deformity

Swan-neck deformity

Fig. 10.1: Finger deformities in rheumatoid arthritis

Wrists

- Synovial swelling at the wrist.
- Loss of flexion and extension.
- Volar subluxation and radial deviation of hand.
- Carpal tunnel syndrome.

Elbows

- Flexion contractures.
- Supination of the hand may be impaired.
- Entrapment neuropathy of ulnar or radial nerves may occur.
- The elbow is the most common site for subcutaneous rheumatoid nodules.

Shoulders

- Involvement of the glenohumeral, acromioclavicular, and thoracoscapular joints is common in advanced RA.
- Limited motion and tenderness.
- Joint destruction may cause rupture of the joint capsule and subluxation of the humerus.

Feet and ankles

- MTP joints are most commonly involved.
- Subluxation of the metatarsal heads into the soles.
- Cock-up and valgus deformities of the toes.
- Ankle and/or tarsal collapse may result in valgus deformity and/or pes planus.

Knees

- Synovial proliferation and effusion.
- Quadriceps atrophy may occur, and a flexion contracture of the knee may develop.
- Advanced disease may produce joint instability and valgus deformity.
- Popliteal (Baker's) cysts may form as a result of effusion or synovial proliferation.

Neck

- Neck pain and stiffness.
- Erosion of bone and ligaments in the cervical spine.
- Atlantoaxial subluxation (C1 on C2).
- Spinal cord compression with neurologic manifestations.

Extra-articular Features

Systemic features

- Low grade fever, weight loss, loss of appetite, and fatigue.

Musculoskeletal

- Muscle wasting, bursitis, tenosynovitis and osteoporosis. Osteoporosis and muscle-wasting result from systemic inflammation.

Skin

- Rheumatoid nodules—these are subcutaneous nodules seen in 25% of patients with RA. They are firm, round masses and vary in size. They seen over the pressure points like the olecranon process, scapula, sacrum, Achilles tendon and the occiput. Visceral structures like heart, lungs and CNS may also be involved. Most skin nodules do not require any treatment. For painful nodules or those that interfere with joint motion or impinge upon

nerves, local injection with a mixture of a steroid and local anesthetic may cause regression.
- Other skin manifestations are ulcers, vasculitis, gangrene and pyoderma gangrenosum.

Eye
- Episcleritis, scleritis
- Scleromalacia is thinning of the sclera—the affected area appears blue or grey (the color of the underlying choroid). No specific treatment is required.
- Keratoconjunctivitis sicca (dry eyes)—this is due to secondary Sjögren's syndrome.

Respiratory
- Pleural effusion is usually bilateral with low pleural fluid glucose.
- Fibrosing alveolitis, nodules, bronchiolitis.
- Caplan's syndrome—this is seen in coal miners who develop multiple nodules in the lungs and interstitial lung disease.

Cardiac
- Pericarditis, myocarditis, and endocarditis.
- Coronary vasculitis—can lead to myocardial infarction.
- Aortitis/aortic regurgitation.
- Conduction disturbances including complete heart block.

Hematological/reticuloendothelial
- Normocytic normochromic anemia.
- Thrombocytosis
- Eosinophilia
- Splenomegaly (Felty's syndrome)

Neurological
- Compression neuropathies—these are due to compression of peripheral nerves by hypertrophied synovium or joint subluxation. For example, carpal and tarsal tunnel syndromes.
- Cervical cord compression—due to subluxation of atlantoaxial joint or at a subaxial level.
- Peripheral neuropathy
- Mononeuritis multiplex

Others
- Systemic vasculitis (skin, CNS, lungs, etc.)
- Amyloidosis is a rare complication of chronic active disease and usually presents with nephrotic syndrome.

Diagnosis of Rheumatoid Arthritis

- Diagnosis should be suspected in any patient who presents with chronic symmetric polyarthritis. American college of rheumatology (ACR) and the European league against rheumatism (EULAR) criteria for the classification of rheumatoid arthritis is as follows:

Feature	Score
Joint involvement	
• 1 large joint (shoulder, elbow, hip, knee, ankle)	0
• 2–10 large joints	1
• 1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2
• 4–10 small joints	3
• >10 joints (at least 1 small joint)	5
Serology	
• Negative RF (rheumatoid factor) and negative ACPA (anti-citrullinated protein antibody)	0
• Low-positive RF or low-positive anti-CCP antibodies (3 times ULN)	2
• High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute-phase reactants	
• Normal CRP and normal ESR	0
• Abnormal CRP or abnormal ESR	1
Duration of symptoms	
• <6 weeks	0
• ≥6 weeks	1

- A score of 6 or more fulfills the requirements for definite rheumatoid arthritis. A score of less than 6 suggests possible RA which requires follow up.

Investigations

- Chronic normocytic, normochromic anemia.
- ESR and CRP are elevated.
- Rheumatoid factor is present in more than 80% of cases.
- Anti-citrullinated peptide (anti-CCP) antibody—this is more specific than rheumatoid factor for the diagnosis of RA.
- Antinuclear antibodies (ANA) can be found in 40% of cases.
- Synovial fluid analysis—usually shows a white cell count of 5000 to 20,000/cu mm, with predominant neutrophils. Synovial fluid glucose is usually normal, but may be low.
- X-rays of the hands, wrists and both feet show peri-articular osteopenia and marginal non-proliferative erosions. Bone erosions may not be seen initially up to 6 months.

Management

- The goals of treatment are: (1) Relief of pain, (2) Reduction of inflammation, (3) Protection of articular structures, (4) Maintenance of function, and (5) Control of systemic involvement.

Pharmacologic Therapy

Analgesics
- Acetaminophen (paracetamol), and NSAIDs (diclofenac, ibuprofen, aceclofenac) have both analgesic and anti-inflammatory properties but do not alter disease outcomes. Opioid analgesics such as propoxyphene,

tramadol, oxycodone, etc. are also useful to control pain. Topical analgesic preparations (e.g. capsaicin or diclofenac) can be combined along with oral agents.

DMARDs (disease-modifying antirheumatic drugs)

- These are slow-acting anti-rheumatic drugs. They can reduce or prevent joint damage, preserve joint integrity and function, and maintain economic productivity. These include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide. Out of these, methotrexate and hydroxychloroquine are commonly used. Other less commonly used DMARDs are gold salts, D-penicillamine, azathioprine, and cyclosporin.
- Methotrexate is given once a week in a dose of 7.5–25 mg per week. Folic acid should be given along with methotrexate to prevent hematological side effect. Hydroxychloroquine is given at a dose of 200–400 mg daily. Sulfasalazine is given at a dose of 1 gm twice daily.

Steroids

- Examples are prednisolone, triamcinolone, etc. These are used to suppress inflammation, and may be administered orally, intravenously, or by intra-articular injection. Prednisolone 7.5 mg/day or less is relatively safe and can be used for extended periods of time. Doses higher than 7.5 mg/day should be used for the shortest time possible.
- The indications for steroids are as follows:
  - As part of combination drug therapy along with NSAIDs and DMARDs during initial control of the disease and during flare ups.
  - Neuropathy and rheumatoid vasculitis.
  - Severe systemic symptoms such as fever and weight loss.

Biological response modifiers

- *Etanercept*: Etanercept is a fusion protein that consists of p75 TNF receptors bound to the Fc portion of IgG. It blocks the activity of TNF by binding to its receptors. Etanercept is effective in many forms of inflammatory arthritis including RA, psoriatic arthritis, and ankylosing spondylitis. It is given as subcutaneous injection once or twice weekly. Redness and swelling can occur at the injection site.
- *Infliximab*: This is a chimeric antibody against TNF. The term "chimeric" refers to the use of both murine and human components of the drug. Infliximab is given as IV infusion every six weeks. Side effects are hypersensitivity reactions, influenza like symptoms and hypotension. Reactivation of tuberculosis can occur.
- Anakinra is a recombinant interleukin-1 receptor antagonist. It is approved for the treatment of RA.
- *Rituximab*: Rituximab is a B cell depleting monoclonal anti-CD20 antibody.

Immunosuppressive agents

- Examples are azathioprine and cyclophosphamide. These are 3rd line agents and are rarely used. They have serious side effects. IV cyclophosphamide may be life-saving in acute vasculitis causing organ damage.

Non-pharmacological measures

- Patient education and counseling—patient should be explained about the chronic nature of disease and the need for long-term therapy. The side effects of drugs should be explained and the need for follow-up stressed.
- Rest—this helps during acute arthritis and during flare ups.
- Exercise—lack of exercise can result in loss of joint mobility, contractures, and muscle atrophy. Patients should exercise regularly to prevent and reverse these problems.
- Physiotherapy—this involves application of heat or cold to relieve pain or stiffness, ultrasound to tenosynovitis, passive and active exercises to improve and maintain joint motion range.

Surgery

- Synovectomy of the wrist or finger tendon sheaths may be required for pain relief or to prevent tendon rupture when medical therapy fails.
- Osteotomy, arthrodesis or arthroplasties may be required in advanced disease when joint destruction and deformities take place.

Q. Felty's syndrome.

- Felty's syndrome refers to severe rheumatoid arthritis (RA) complicated by neutropenia and splenomegaly. Although the pathophysiology of Felty's syndrome is not fully understood, evidence points to splenic sequestration and subsequent neutrophil destruction.

Clinical Features

- Felty's syndrome is characterized by rheumatoid arthritis, neutropenia, and splenomegaly.
- Both articular and extra-articular features of rheumatoid arthritis are more severe in Felty's syndrome.
- Neutropenia (neutrophil count <2000/mm^3) predisposes to recurrent bacterial infections. Respiratory tract and skin infections due to bacteria are most common.
- Splenomegaly can be detected clinically in most patients and sometimes can be massive.

Investigations

- Low neutrophil count (<2000/mm^3) is required for the diagnosis of Felty's syndrome.

- Peripheral blood smear to rule out any other hematological abnormality.
- Bone marrow shows myeloid hyperplasia with a relative excess of immature forms.
- Ultrasound abdomen may be required to demonstrate splenomegaly.
- Autoantibodies other than rheumatoid factor (e.g. ANA, anti-histone antibodies, ANCA, anti-dsDNA antibodies) are commonly present in Felty's syndrome.

Management

- Treatment is generally same as for rheumatoid arthritis.
- G-CSF (granulocyte colony stimulating factor) may be required to rapidly reverse neutropenia in patients with life-threatening or refractory bacterial infection.
- Splenectomy is required for severe persistent neutropenia and severe thrombocytopenia due to hypersplenism.

Q. Juvenile idiopathic arthritis (juvenile rheumatoid arthritis).

Q. Still's disease.

- Juvenile idiopathic arthritis (JIA) is a group of rheumatic diseases that begins at or before age 16.
- JIA is divided into many subtypes based on clinical and laboratory features is as follows:
  - *Oligoarticular JIA*: Most common form and affects young girls. It involves less than five joints after six months of illness. Arthritis causes joint stiffness, swelling, effusion, pain, and tenderness.
  - *Polyarticular JIA*: Refers to involvement of five or more joints after six months of illness. Arthritis tends to be symmetric and frequently involves the small joints.
  - *Enthesitis-related arthritis*: Involves arthritis and enthesitis (painful inflammation at the insertion of tendons and ligaments). Some of these patients may develop classic features of one of the spondyloarthropathies such as ankylosing spondylitis or reactive arthritis.
  - *Psoriatic JIA*: Typically occurs in young girls and is associated with psoriasis. Arthritis is frequently oligoarticular.
  - *Undifferentiated JIA* is diagnosed when patients do not meet criteria for any one category or meet criteria for more than one.
  - *Systemic JIA (Still's disease)*: This is the least common form. Here there is skin rash and intermittent fever in addition to arthritis. It is called adult-onset Still's disease if it occurs over the age of 16. Children often appear quite ill with high spiking fevers, rashes, leukocytosis, and anemia. Rash is macular, pink and often found in the axilla and waist, but may be present anywhere on the body. Other features are splenomegaly, hepatomegaly, lymphadenopathy, pericarditis, pleural effusion, etc.

Treatment

- Treatment is similar to rheumatoid arthritis. Disease modifying antirheumatic drugs (DMARDs), such as methotrexate, hydroxychloroquine and the biologic agents (e.g. etanercept, anakinra) are used.
- NSAIDs are used to control pain and inflammation.
- Corticosteroids are useful in severe disease.

Q. Rheumatoid factor (RF).

- Rheumatoid factor (RF) is an antibody directed against the Fc portion of IgG.
- RF is usually of IgM class, although IgG and IgA are also seen rarely.
- RF was first identified in patients with rheumatoid arthritis but also occurs in other conditions and in some normal adults.
- RF is not diagnostic of rheumatoid arthritis. It has more sensitivity than specificity in the diagnosis of rheumatoid arthritis. Its principal use is as a prognostic marker; a high titer at presentation associates with a poorer prognosis.

Diseases Associated with RF Positivity

Rheumatic disorders
- Rheumatoid arthritis
- Sjögren's syndrome
- Mixed connective tissue disease
- Mixed cryoglobulinemia
- SLE
- Polymyositis/dermatomyositis

Nonrheumatic disorders
- Chronic infections (subacute bacterial endocarditis, hepatitis B or C virus infection).
- Sarcoidosis
- Malignancy
- Primary biliary cirrhosis.

Healthy individuals
- RF can be positive in up to 4% of healthy individuals.

Q. Anti-cyclic citrullinated peptide (anti-CCP) antibody.

- Citrullinated peptide is found in the keratin and synovium. Antibodies directed against these peptides are called anti-CCP antibodies.

- Anti-CCP antibodies are helpful in the diagnosis of rheumatoid arthritis. Anti-CCP antibodies are more specific but less sensitive than rheumatoid factor in the diagnosis of RA. It has a sensitivity of around 60% and specificity of around 90% for RA. Testing for both rheumatoid factor and anti-CCP is more useful in excluding the diagnosis of RA than either of the tests alone. Anti-CCP is especially useful in early diagnosis of RA when classic features are not present.
- Anti-CCP antibody positive patients with RA are at increased risk of more rapid radiologic progression and progressive joint damage.
- Anti-CCP antibody may also be positive in other conditions such as active tuberculosis, SLE, Sjögren's, polymyositis, dermatomyositis, and scleroderma. However, titers are less in these conditions than in RA.

Q. What are spondyloarthropathies (seronegative spondyloarthropathies)? Discuss the pathology and general features of spondyloarthropathies.

- The term, spondyloarthritis (formerly spondyloarthropathy), is used to refer to a group of inflammatory joint diseases sharing similar pathogenesis, distinct from RA. They usually involve both spine and peripheral joints (spondylo means spine and arthro means joints).
- They have overlapping articular and extra-articular features.
- They have strong association with HLA-B27.
- Rheumatoid factor (RF) is negative. Hence, they are also known as seronegative spondyloarthropathies.
- They are:
  - Ankylosing spondylitis (AS)
  - Reactive arthritis (ReA) including Reiter's syndrome
  - Psoriatic arthritis
  - Spondyloarthropathy associated with inflammatory bowel disease
  - Undifferentiated spondyloarthritis

Pathology

- There is non-specific synovitis in the joints which is often indistinguishable from rheumatoid synovitis.
- However, a distinctive feature is extrasynovial inflammation involving tendon insertion sites (enthesitis), joint capsule, periarticular periosteum, cartilage and subchondral bone.
- The inflammation resolves leaving behind fibrosis which may calcify and ossify leading to joint fusion. In the spine, periarticular osteitis and periostitis may result in bony spurs that bridge adjacent vertebral bodies (syndesmophytes) or protrude at sites of ligament attachment (e.g. calcaneal or olecranon 'spurs').
- Large central cartilaginous joints (sacroiliac, intervertebral, symphysis pubis) are particularly involved.

Clinical features common to seronegative spondyloarthropathies

- Asymmetrical inflammatory oligoarthritis (lower limb > upper limb)
- Involvement of spine (spondylitis) and sacroiliac joints
- Inflammation of tendon insertion sites (enthesitis)
- Strong association with HLA-B27 and tendency for familial aggregation
- Rheumatoid factor is usually negative
- Absence of nodules and other extra-articular features of RA

Extra-articular features

- *Inflammation of mucosal surface*: Conjunctivitis, buccal ulceration, urethritis, prostatitis, bowel ulceration
- *Inflammation in the eyes*: Uveitis
- Pustular skin lesions, nail dystrophy
- Aortic root fibrosis (aortic incompetence, conduction defects)
- Erythema nodosum

Q. Discuss the etiology, clinical features, investigations and management of ankylosing spondylitis.

- Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton characterized by back pain, progressive stiffening and fusion of the spine. It has predilection for the sacroiliac joints and spine.
- Ankylosis refers to a fibrous or bony bridging of joints. In the spine this includes bridging of one or more intervertebral discs.

Etiology

- Exact etiology is unknown.
- Genetic factors—most patients are HLA-B27 positive. Close relatives of patients with AS have increased risk of developing AS.
- Infections—increased fecal carriage of *Klebsiella aerogenes* occurs in patients with ankylosing spondylitis.

Clinical Features

- It characteristically affects young adults with a peak age of onset between 20 and 30 years.
- Males are more commonly affected (male : female ratio 3 : 1).

Articular Features

- Spine and lumbosacral joints are mainly involved.
- Insidious onset of low back pain and stiffness. Pain and stiffness are worse in the morning and after inactivity

and are relieved by movement. Lumbosacral area is usually the first and worst affected region, but rarely thoracic or cervical spine can get affected first.

- As the disease progresses, whole spine is affected. As the spine becomes progressively ankylosed, spinal rigidity and secondary osteoporosis predispose to spinal fracture, presenting as acute, severe, well-localized pain. Secondary spinal cord compression is a rare complication.
- Examination shows restricted spinal mobility in all directions, pain on sacroiliac compression, and diminished chest expansion. Increasing flexion of the neck, increased thoracic kyphosis and loss of normal lumbar lordosis may lead to a stooped posture.
- Peripheral arthritis is seen in 30% of patients. Hips, knees, ankles and shoulders are mainly involved. Peripheral arthritis may precede spinal involvement in 10% of cases.

Extra-articular Features

- Enthesitis—inflammation in tendon or ligament insertion sites (Achilles tendon, iliac crest and greater trochanter)
- Eye—anterior uveitis (25%) and conjunctivitis (20%).
- Prostatitis (80% men).
- CVS—aortic regurgitation, pericarditis, MVP).
- RS—atypical upper lobe pulmonary fibrosis.
- CNS—cervical myelopathy (secondary to atlantoaxial dislocation), cauda equina syndrome.
- Kidneys—IgA nephropathy, secondary amyloidosis.
- GIT—mucosal ulcers.

Investigations

- ESR and CRP are usually elevated.
- Rheumatoid factor is negative or present in low titre.
- HLA B27 is usually positive.
- Radiographs—sacroiliac joint is usually first involved. X-ray of sacroiliac joint may show irregularity and loss of cortical margins, widening of the joint space, sclerosis, narrowing and fusion. Lateral thoracolumbar spine X-ray may show anterior 'squaring' of vertebrae due to erosion and sclerosis of the anterior corners, bridging syndesmophytes, ossification of the anterior longitudinal ligament and facet joint fusion. All these changes produce the typical 'bamboo' spine. Erosive changes may be seen in the symphysis pubis, the ischial tuberosities and peripheral joints. Osteoporosis and atlantoaxial dislocation can occur.

Management

- The goals of treatment are to relieve pain and stiffness, maintain skeletal mobility and prevent deformity.

Non-pharmacological Measures

- Education of the patient about the disease.
- Regular daily back extension exercises, including a morning 'warm-up' routine.
- Avoid prolonged periods of inactivity.
- Poor bed and chair posture must be avoided.

Drug Therapy

- *NSAIDs*—relieve the symptoms but do not alter the course of the disease.
- A long-acting NSAID at night is particularly helpful for marked morning stiffness.
- *Antirheumatic drugs*—sulfasalazine, methotrexate or azathioprine may control peripheral arthritis but have a little effect on spine inflammation.
- *Anti-TNF agents*—etanercept, infliximab, and adalimumab have been shown to improve signs and symptoms of AS, including spinal mobility.
- Steroids—local corticosteroid injections are helpful in persistent plantar fasciitis and enthesitis. Oral steroids are useful in acute uveitis but should otherwise be avoided.

Surgery

- Severe hip, knee or shoulder restriction may require surgery. Total hip replacement (total hip arthroplasty), cervical fusion for atlantoaxial subluxation, and wedge osteotomy for severe flexion deformities of the spine are the surgical procedures that may be required.

Q. Discuss the etiology, clinical features, investigations, and management of reactive arthritis.

Q. Reiter's syndrome.

- The term "reactive arthritis" refers to an arthritis that is associated with a recent or co-existing extra-articular infection usually gastrointestinal or genitourinary infections.
- Reiter's syndrome refers to the triad of reactive arthritis, urethritis, and conjunctivitis.

Etiology

- *Gastrointestinal infections*: Salmonella, Shigella, Campylobacter and Yersinia.
- *Genitourinary infections*: Chlamydia, *N. gonorrhea*.
- *Genetic predisposition*: The prevalence of the HLA-B27 allele in patients is 63 to 96% vs 6 to 15% in healthy white controls, thus supporting a genetic predisposition.

Clinical Features

- Reactive arthritis commonly affects young men (sex ratio 15:1) aged 16–35 years. However, it may occur at any age.

- Presentation is usually acute onset oligoarthritis affecting the large and small joints of the lower limbs 1 to 3 weeks following sexual exposure or an attack of dysentery. Symptoms and signs of urethritis or conjunctivitis may be minimal or absent and there may be no clear history of prior dysentery.
- Extra-articular features are Achilles tendonitis, plantar fasciitis, circinate balanitis, keratoderma blennorrhagica, nail dystrophy and buccal ulcers. Circinate balanitis is superficial erosions in a circular pattern on the coronal margin of the glans penis. Keratoderma blennorrhagica are hyperkeratotic skin lesions with desquamating margins.
- Systemic features like fever, fatigue and weight loss can occur.

Investigations

- ESR and CRP are raised.
- Normocytic, normochromic anemia.
- Synovial fluid analysis shows features of inflammation such as low viscosity, turbid appearance and presence of giant macrophages (Reiter's cells).
- Urine culture may show *N. gonorrhea* or Chlamydia.
- Stool culture may grow the causative organism but are usually negative by the time arthritis develops.
- Serologic testing—detection of antibodies against the organism may help confirm previous dysentery.
- Rheumatoid factor and ANA are negative.
- *Radiographic features*: Initially there are no changes. With chronic disease, periarticular osteopenia, joint space narrowing and marginal proliferative erosions may develop. Periostitis, especially of metatarsals, phalanges and pelvis, and large 'fluffy' calcaneal spurs may be seen. Asymmetrical or unilateral sacroiliitis and syndesmophytes can occur.

Management

- NSAIDs—control the pain and inflammation of arthritis.
- Steroids—intra-articular or local corticosteroid injections are helpful in relieving the symptoms of arthritis or enthesitis. Systemic steroids are used for anterior uveitis.
- Antirheumatic drugs—sulfasalazine has been shown to be effective in reactive arthritis. Azathioprine or methotrexate may be required in severe progressive arthritis and intractable keratoderma blennorrhagica.
- Antibiotics are used to treat acute infection. Chlamydial urethritis is treated with doxycycline.

Q. Discuss the clinical features, diagnosis, and management of psoriatic arthritis.

- Psoriatic arthritis occurs in about 1 in 1000 of the population and in 7% of patients with psoriasis.
- Psoriatic arthritis usually occurs in patients with current or previous skin psoriasis. In some patients it may precede the onset of psoriasis or may start simultaneously with psoriasis. Rarely there may be arthritis without skin lesions.
- The onset is usually between 25 and 40 years of age.
- The exact cause of psoriatic arthritis is unknown. However, genetic, immunologic, and environmental factors all play a role in the causation of the disease.

Clinical Features

Articular Features

- Psoriatic arthritis usually presents as asymmetrical oligoarthritis. Both upper and lower limb joints can be affected. The distal interphalangeal (DIP) joints of fingers and toes are especially affected. Hand deformity often results from tenosynovitis and soft tissue contractures. Knees are affected often with very large effusions.

Extra-articular Features

- Enthesitis affects Achilles tendon, plantar fascia and the pelvic bones.
- Tenosynovitis affects the flexor tendons of the hands, the extensor carpi ulnaris, or other sites.
- Dactylitis is defined as uniform swelling of the soft tissues of the digits. Such affected digits are also called "sausage digit".
- Skin lesions—plaques with silvery white scales.
- Nail changes include pitting, onycholysis, nailbed hyperkeratosis, and splinter hemorrhages. Conjunctivitis and uveitis.

Investigations

- ESR and CRP are elevated.
- Rheumatoid factor and ANA are usually negative.
- X-rays may be normal or show erosive changes with new bone formation in the distal joints.
- MRI is more sensitive than plain X-rays in detecting articular, periarticular, and soft-tissue inflammation.

Management

- *General measures*: Regular exercise and attention to posture should be prescribed as in those with spondylitis. Splints and prolonged rest are avoided because of the increased tendency to fibrous and bony ankylosis.
- *NSAIDs*: These are first choice and help in pain relief and control inflammation.
- *Second-line drugs*: These are indicated for persistent arthritis. Examples are sulfasalazine methotrexate or azathioprine. Antimalarial agents such as hydroxychloroquine should be avoided because it can exacerbate psoriatic skin lesions.
- *Surgery*: May be required for severe joint destruction causing immobility.

Q. Arthritis associated with inflammatory bowel disease (enteropathic arthritis).

- "Enteropathic arthritis" refers to the arthropathies associated with Crohn's disease or ulcerative colitis.
- It is an acute inflammatory oligoarthritis mainly involving large lower limb joints (i.e. knees, ankles, hips) but upper limb joints such as wrists, elbows and small joints of the fingers and toes can also be involved. Sacroiliac and spinal joints are also involved.
- Onset of arthritis may coincide with exacerbations of inflammatory bowel disease.

Treatment

- NSAIDs
- Sulfasalazine
- Azathioprine and methotrexate in refractory cases.

Q. Comparison of various spondyloarthropathies.

Feature	Ankylosing spondylitis	Reactive arthritis	Psoriatic arthritis	Enteropathic arthritis
Age of onset	Late teens to early adulthood	Late teens to early adulthood	35–40 years	Any age
Male to female ratio	More common in males	More common in males	Equal	Equal
Sacroiliac joint involvement	Common	Less common	Less common	Rare
Spondylitis	Common	Less common	Less common	Rare
Peripheral joint involvement	Rare	Common	Common	Common
Course of disease	Chronic	Acute or chronic	Chronic	Acute or chronic
HLA-B27	95%	30–60%	20%	20%
Enthesitis	Less common	Common	Less common	Less common
Common extra-articular involvement	Eye, heart	Eye, urinary tract, GIT	Skin, nails, eye	GIT, eye

Q. Enumerate the crystal induced arthritis.

Q. Discuss the etiology, clinical features, investigations and management of gout.

- Crystal induced arthritis is due to intra-articular deposition of crystals which are as follows:
  - *Gout*, due to uric acid.
  - *Pseudogout*, due to calcium pyrophosphate.
  - *Acute arthritis in dialysis patients*: Calcium oxalate.

Gout

- Gout refers to disease that occurs in response to the presence of monosodium urate (MSU) crystals in joints, bones, and soft tissues.

Etiology

- It occurs due to hyperuricemia (normal value less than 7 mg/dl). Causes of hyperuricemia are as follows:

Increased Intake

- Intake of purine-rich foods (e.g. liver, kidney, asparagus, meat, mushrooms, mussels, sardines).
- Beer is particularly rich in guanosine, a purine nucleoside.

Increased production

- Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency
- Phosphoribosylpyrophosphate (PRPP) synthetase overactivity
- Glucose-6-phosphatase deficiency (glycogen storage disease, type I)
- Increased nucleoprotein turnover in hematologic conditions: Lymphoma, leukemia, hemolytic anemia
- Increased rates of cellular proliferation and cell death: Psoriasis, cancer chemotherapy, radiation therapy, malignancies
- Obesity

Decreased renal excretion

- Inherited isolated renal tubular defect ('under-excretors')
- Renal failure
- Lead poisoning
- Diabetic ketoacidosis
- Lactic acidosis
- Hypothyroidism
- Drugs (thiazides, pyrazinamide, cyclosporine)

Epidemiology

- Gout is more common in males (male : female ratio >10 : 1). Prevalence increases with age and increasing serum uric acid concentration.

Clinical Features

- Three types of clinical presentation can be recognized in the natural history of gout.
  1. Acute gouty arthritis
  2. Recurrent and chronic gout
  3. Chronic tophaceous gout

Acute Gout

- The typical attack of acute gouty arthritis, includes the following clinical features:
  - Usually involves single distal joint. Most commonly involved joint is base of the great toe (first metatarsophalangeal joint, known as podagra), or the knee. Other common sites (in order of decreasing frequency) are the ankle, midfoot, knee, small joints of hands, wrist and elbow. Spine and large proximal joints are rarely involved and never as the first site.
  - Onset of arthritis is sudden and there is severe pain, redness, and swelling of the affected joints. Complete resolution occurs within a few days to several weeks.
  - There may be periarticular swelling and erythema, accompanying fever, malaise and even confusion, especially if a large joint such as the knee is involved. As the attack subsides, pruritus and desquamation of overlying skin are common.
  - Acute attacks may also manifest as bursitis, tenosynovitis or cellulitis.

Recurrent and Chronic Gout

- After an acute attack some people never have a second episode. However, some may have a second attack usually within 1 year and the frequency of attacks gradually increases with time leading to joint damage and chronic pain.

Chronic Tophaceous Gout

- Tophaceous gout is characterized by collections of solid urate in connective tissues (which may be calcified).
- These collections produce irregular firm nodules ('tophi') at the usual sites for nodules around extensor surfaces of fingers, hands, forearm, elbows, Achilles tendons and sometimes the helix of the ear. They may be clinically visible or detected by imaging.
- Tophi are usually painless and nontender. Large tophi may ulcerate, discharging white gritty material.

Renal and Urinary Tract Manifestations

- Uric acid stones may form and cause renal colic.
- Urate crystal deposition in the interstitium of the medulla and pyramids leads to chronic inflammation, fibrosis, glomerulosclerosis and secondary pyelonephritis.

Investigations

- Polarizing microscopy—definitive diagnosis requires identification of monosodium urate crystals in the aspirate from a joint, bursa or tophus.
- Histologic examination—birefringent urate crystals may be visible in biopsy specimens.
- Uric acid levels in the blood are elevated (>7 mg/dl). However, occasionally it can be normal (<7 mg/dl).
- 24-hour urinary uric acid excretion—can identify uric acid over-producers.
- Urea, creatinine should be measured to rule out renal dysfunction.
- Complete blood picture, ESR and peripheral blood smear should be done to rule out any myeloproliferative disorders.
- X-rays—can assess the degree of joint damage. In early disease they are usually normal, but in advanced disease, narrowing of joint space, sclerosis, cysts and osteophyte (changes of OA) may develop. Calcified tophi may be visible on X-rays.

Management

Acute Attack

- Oral NSAID (e.g. naproxen, diclofenac, indomethacin) can give effective pain relief and is the standard treatment.
- Oral colchicine is effective in acute attacks but can cause vomiting and diarrhea.
- Steroids, either oral or intra-articular can give rapid relief. Can be used if symptoms are very severe.
- Aspiration of the joint gives instant relief and, when combined with an intra-articular corticosteroid injection effectively aborts the attack.
- Note that allopurinol and uricosuric drugs should not be given during acute attack because they can worsen the attack.

Long-term Management

- *Lifestyle changes*: Correct obesity and reduce alcohol consumption. Avoid high purine diet (seafood, red meat and offal). Stop diuretics if possible.
- *Hypouricemic drugs*: Allopurinol inhibits xanthine oxidase and reduces conversion of hypoxanthine and xanthine to uric acid. Dosage is 100–300 mg daily. The sharp reduction in tissue uric acid levels after allopurinol therapy can dissolve monosodium urate crystals and trigger acute attacks. This risk can be minimized by starting at low dose (100 mg). Since it can exacerbate acute attacks, it should be withheld till the acute attack subsides. Febuxostat, is a new drug and is a nonpurine

selective inhibitor of xanthine oxidase. Febuxostat is given orally and is metabolized mainly in the liver. In contrast, allopurinol and its metabolites are excreted primarily by the kidney. Therefore, febuxostat can be used in patients with renal impairment with no dosage adjustment.

- The goal of treatment is to reduce serum uric acid level to lower half of normal range. In most cases allopurinol will need to be continued indefinitely.
- Uricosuric drugs such as probenecid or sulfinpyrazone also have equal efficacy to allopurinol but require more frequent dosing. Uricosurics are contraindicated in over-producers (they already have gross uricosuria), those with renal impairment (ineffective), and in patients with urolithiasis (increased stone formation).
- Asymptomatic hyperuricemia need not be treated unless the levels are very high (>10 mg/dl) or there is strong family history of gout or urolithiasis.

Q. Calcium pyrophosphate crystal (CPP) deposition disease; pseudogout; chondrocalcinosis.

- Pseudogout is a form of arthritis that develops in some people in response to the presence of calcium pyrophosphate (CPP) crystals.
- The term "pseudogout" is commonly used because the symptoms of the disorder are very similar to those caused by gout. Chondrocalcinosis refers to crystal deposition in hyaline and/or fibrocartilage without signs of arthritis.
- Pseudogout is rare under the age of 55. The knee (hyaline cartilage and menisci) is the most commonly affected site, followed by the wrist and pelvis.

Etiology

- Aging (sporadic)
- Joint trauma (is a risk factor for crystal deposition)
- Familial (familial chondrocalcinosis)
- Metabolic diseases (hemochromatosis, hyperparathyroidism, hypophosphatasia, hypomagnesemia, Wilson's disease)

Pathogenesis

- The exact cause of crystal formation is not clear. The crystals first develop in the joint cartilage and eventually move to synovium and joint fluid where they cause inflammation. This causes pain and swelling.

Clinical Features

Asymptomatic Disease (Chondrocalcinosis)

- There is radiographic evidence of CPP crystal deposition in the cartilage of joints without any symptoms.

Acute Arthritis (Pseudogout)

- This is the most common cause of acute monoarthritis in the elderly. Knee is the commonest site, followed by wrist, shoulder, ankle and elbow.
- It may be the first presentation of pseudogout. Joint trauma, intercurrent illness or surgery may trigger an acute attack of arthritis in asymptomatic patients.
- Acute attack resembles acute gout and is characterized by severe pain, stiffness and swelling of affected joint. Pseudogout should be differentiated from acute gouty arthritis and septic arthritis.

Chronic Arthritis

- This is commonly seen in elderly women. Symptoms are chronic pain, early morning stiffness, and functional impairment. Acute attacks may be superimposed on chronic arthritis.

Investigations

- Demonstration of CPP crystals in synovial fluid.
- X-rays may show chondrocalcinosis.
- Screening for metabolic or familial causes should be done in young patients.

Management

- Aspiration of joint effusion quickly reduces pain and may alone be sufficient.
- Intra-articular injection of corticosteroid.
- Oral NSAIDs and colchicine.

Q. Discuss the etiology, pathogenesis, clinical features, diagnosis, and management of systemic lupus erythematosus (SLE).

- Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of autoimmune etiology which affects multiple organ systems. It is the most common multisystem connective tissue disease.
- Immunologic abnormalities, especially the production of a number of antinuclear antibodies, are another prominent feature of the disease.
- The prevalence is 50 to 150 per lakh population. 90% of affected patients are females, with peak onset in the second and third decades. It is more common in urban than rural areas.

Etiology

- Exact etiology is unknown. Thought to be autoimmune.

- *Genetic factors*: There is a high concordance rate of SLE in monozygotic twins. It is more common in relatives of SLE patients. Risk of SLE is increased in those with HLA-B8, HLA-DR2, and HLA-DR3.
- *Hormonal factors*: Altered sex hormone levels may predispose to the development of SLE. Use of estrogen-containing contraceptive agents is associated with increased risk of developing SLE.
- *Immune abnormalities*: SLE is primarily a disease with abnormalities in immune regulation. Affected patients are not tolerant to their self-antigens, and consequently develop an autoimmune response. Phagocytosis and clearing of immune complexes and of apoptotic cells are defective in SLE.
- *Environmental factors*: Some viruses, ultraviolet rays and silica dust may increase the risk of developing SLE.

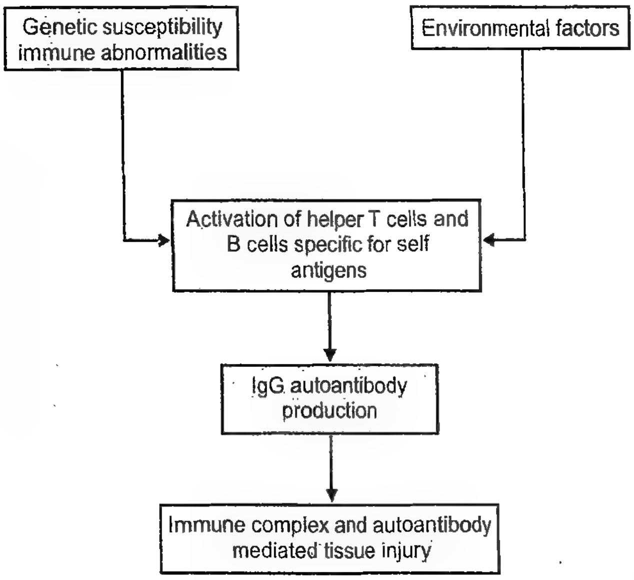


Fig. 10.2: Pathogenesis of SLE

Pathogenesis

- Many components of intracellular and intranuclear machinery act as autoantigens in SLE. In normal health these antigens are 'hidden' from the immune system and do not provoke an immune response.
- Interactions between susceptibility genes and environmental factors result in abnormal immune responses.
- This abnormal immune response results in the production of pathogenic autoantibodies and immune complexes that deposit in tissues, activate complement, cause inflammation, and over time lead to irreversible organ damage.

Clinical Features

- SLE affects almost all the organ systems.

Constitutional Symptoms

- Fatigue, fever, weight loss and mild lymphadenopathy.

Raynaud's Phenomenon

- Cold or emotion-induced color changes of the digits of the hands and/or feet is a frequent problem.

Musculoskeletal Features

- Joint symptoms occur in over 90% of patients with SLE. The arthritis tends to be migratory and asymmetrical. Only a few joints are usually affected, especially those of the hands. Joint deformities are usually rare.
- Avascular necrosis.
- Tenosynovitis.

Mucocutaneous Features

- The most common lesion is butterfly rash (erythema over the cheeks and nose, which appears after sun exposure). It spares the nasolabial folds. The absence of papules and pustules helps distinguish SLE from rosacea.
- Discoid rashes are characterized by hyperkeratosis and follicular plugging with a tendency to scar.
- Vasculitic skin lesions may include mottled erythema on the palms and fingers, periungual erythema, nail-fold infarcts, urticaria, and palpable purpura.
- Other skin manifestations include livedo reticularis, photosensitivity, Raynaud's phenomenon, and alopecia (hair loss).
- Mucous membrane manifestations are painless oral and/or nasal ulcers.

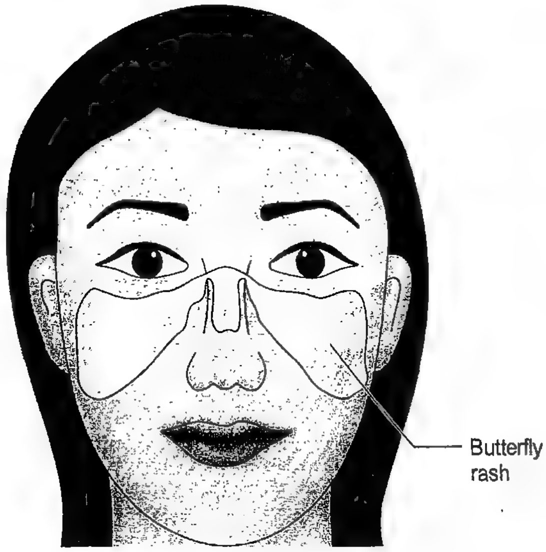


Fig. 10.3: Butterfly rash in SLE

Renal Features

- Kidney is the most commonly involved visceral organ in SLE.
- Initially it may be asymptomatic. Hence, regular urine analysis for proteinuria, and serum creatinine measurements are important.
- Proliferative glomerulonephritis (lupus nephritis) characterized by hematuria, proteinuria and urinary casts.

Cardiovascular Features

- Pericarditis leading to chest pain and pericardial effusion.
- Myocarditis and sterile Libman-Sacks endocarditis. Libman-Sacks endocarditis is characterized by non-infectious vegetations, formed as a result of procoagulability in association with antiphospholipid antibodies.
- Increased risk of venous thromboembolism due to the presence of antiphospholipid antibodies.
- Coronary vasculitis causing angina is rarely reported.

Pulmonary Features

- Pleuritis and pleural effusion.
- Pneumonitis.
- Interstitial lung disease.
- Pulmonary hypertension.
- Alveolar hemorrhage.
- Shrinking or vanishing lung syndrome.
- Pulmonary embolism.

Neuropsychiatric Features

- Fatigue, headache, poor concentration.
- Visual hallucinations.
- Chorea (also associated with antiphospholipid antibody syndrome).
- Organic psychosis.
- Transverse myelitis.
- Lymphocytic meningitis.
- Seizures.

Hematological Features

- Coombs' positive hemolytic anemia.
- Pancytopenia (anemia, leukopenia and thrombocytopenia) due to antibody-mediated destruction of peripheral blood cells.
- Splenomegaly and lymphadenopathy.

Gastrointestinal Features

- Nonspecific abdominal pain.
- SLE vasculitis can lead to pancreatitis, peritonitis, and colitis.
- Mesenteric vasculitis.
- Hepatosplenomegaly.

Ophthalmologic Features

- Keratoconjunctivitis sicca due to secondary Sjögren's syndrome.
- Rare features are cotton wool exudates due to retinal vasculitis, episcleritis or scleritis, and uveitis.

Diagnosis

Investigations

- Complete blood count and differential count: Anemia or pancytopenia is seen.
- Serum creatinine, urine analysis with micrscopy, and 24-hour urinary protein excretion to rule out renal involvement.
- ESR, CRP are elevated and complement levels (C3, and C4) are decreased.
- Autoantibody testing—antinuclear antibodies (ANA), antiphospholipid antibodies, antibodies to double-stranded DNA and anti-Smith (Sm) antibodies may be positive. Antinuclear antribody (ANA) test is the best diagnostic test for SLE. ANA is positive in significant titer (usually 1:160 or higher) in virtually all patients with SLE. However, ANA is not specific for SLE and it can be positive in Sjögren's syndrome, scleroderma, and rheumatoid arthritis. Anti-ds DNA and anti-Sm antibodies—these two autoantibodies are highly specific for SLE. Other antibodies that can be positive in SLE are antibodies to single-stranded DNA and nucleoprotein (NP), antibodies to ribonucleoprotein (anti-RNP), antibodies to Ro (SS-A) and La (SS-B).
- *Chest X-ray*: To look for pneumonitis, interstitial lung disease, etc.
- CT or MRI brain in people who present with seizures.
- Biopsy—biopsy of an involved organ (e.g. skin or kidney) is necessary in some cases.

Diagnostic Criteria

- Revised American College of Rheumatology (ACR) criteria for SLE. (Remember the mnemonic SOAP BRAIN MD made from the first letter of following criteria in the left column).
- A patient is classified as having SLE if the patient has biopsy-proven lupus nephritis with ANA, or anti-dsDNA antibodies or if the patient satisfies 4 of the following 11 diagnostic criteria (*see* below), including at least 1 clinical and 1 immunologic criterion.

Serositis	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or Pericarditis—documented by EKG, rub or evidence of pericardial effusion
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Blood disorder	Hemolytic anemia, or Leukopenia—less than 4,000/mm³ on 2 occasions, or Lymphopenia—less than 1,500/mm³ on 2 occasions, or Thrombocytopenia—less than 100,000/mm³ in the absence of offending drugs
Renal disorder	Persistent proteinuria greater than 0.5 grams per day or >3+ if quantitation not performed Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Antinuclear antibody	An abnormal titer of antinuclear antibody in the absence of drugs known to be associated with "drug-induced lupus" syndrome
Immunologic disorders	Positive antiphospholipid antibody or Anti-DNA—antibody in abnormal titer or Anti-Sm
Neurologic disorder	Seizures or psychosis—in the absence of offending drugs or known metabolic derangements
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions

Management

- Educate the patient to avoid sun and UV light exposure, and to use sun block preparations.
- NSAIDs are enough for mild joint pain.
- Hydroxychloroquine (200–400 mg daily) is used for more troublesome cutaneous and joint symptoms.
- Steroids—short courses of oral steroids are required for mild to moderate disease activity (e.g. rashes, synovitis, pleuropericarditis). High dose steroids (oral prednisolone 40–60 mg daily or IV methylprednisolone 500 mg–1 g) in combination with pulse IV cyclophosphamide is required for life-threatening disease (i.e. renal, cerebral involvement, systemic vasculitis, diffuse alveolar hemorrhage).
- Immunosuppressive drugs (azathioprine, methotrexate, cyclosporin, tacrolimus, mycophenolate mofetil)—these are useful either alone or in combination with steroids for severe but non-life-threatening manifestations or as step-down therapy after cyclophosphamide.
- Belimumab: The monoclonal antibody belimumab, a B-lymphocyte inhibitor, has been found to reduce disease activity and number of severe flares and steroid use in patients with SLE when used in combination with standard therapy.
- Anticoagulants, such as warfarin is required lifelong for patients with the antiphospholipid antibody syndrome with thrombotic events.

Q. Autoantibodies in SLE.

Test	Description
ANA (antinuclear antibody)	Antinuclear antibodies are autoanti bodies that bind to contents of the cell nucleus. ANA is used as a screening test for diagnosing connective tissue diseases; ANA is positive in significant titre (usually 1:160 or higher) in virtually all patients with SLE. However, ANA is not specific for SLE and it can be positive in Sjögren's syndrome, scleroderma, and rheumatoid arthritis; not diagnostic without clinical features. There are many subtypes of ANA which are anti-dsDNA, anti-Sm, anti-SSA, anti-SSB (Sjögren's syndrome B, anti-ribosomal P, anti-RNP (ribonucleic protein), etc.
Anti-ds DNA (double-stranded DNA)	High specificity; sensitivity only 70%. Anti-dsDNA levels correlate with disease activity in SLE; high levels indicate more active lupus.
Anti-Sm (Smith)	Most specific antibody for SLE; only 30–40% sensitivity. They are associated with central nervous system involvement, kidney disease, lung fibrosis and pericarditis in SLE, but they are not associated with disease activity.
Anti-SSA (Sjögren syndrome A) or Anti-SSB (Sjögren syndrome B)	Present in 15% of patients with SLE and other connective tissue diseases such as Sjögren's syndrome.
Anti-ribosomal P	Uncommon antibodies that may correlate with risk for CNS disease, including increased risk of psychosis.

(contd.)

Anti-RNP (ribonucleic protein)	Presence of this antibody indicates mixed connective tissue disease with overlap SLE, scleroderma, and myositis.
Anticardiolipin	These are IgG/IgM antiphospholipid antibodies used to screen for antiphospholipid antibody (APLA) syndrome which can occur in SLE.
Lupus anticoagulant (LA)	LA is tested along with anticardiolipin antibody to diagnose APLA. It can be positive in SLE. Lupus anticoagulant is a misnomer, as it is actually a prothrombotic agent.
Direct Coombs' test	Positive test indicates presence of antibodies on RBCs.
Anti-histone	Drug-induced lupus ANA antibodies are often of this type (e.g. with procainamide or hydralazine. p-ANCA is positive in minocycline-induced drug-induced lupus).

Q. Raynaud's syndrome (Raynaud's phenomenon).

- Raynaud's syndrome is characterized by recurrent vasospasm of the fingers and toes on exposure to cold temperature or emotional stress. It is due to an exaggerated vascular response and was first described by Maurice Raynaud, a medical student.

Types

Primary Raynaud's Syndrome

- This is characterized by the occurrence of the vasospasm alone, without any underlying disorder.

Secondary Raynaud's Syndrome

- This is occurrence of the vasospasm which is associated with an underlying disorder, most commonly an autoimmune disease.

Etiology

- The cause of primary Raynaud's syndrome remains unknown. The causes of secondary Raynaud's syndrome include the following:
- *Autoimmune diseases*: Progressive systemic sclerosis (scleroderma), SLE, mixed connective tissue disease, dermatomyositis and polymyositis, rheumatoid arthritis, Sjögren's syndrome, vasculitis.
- *Infectious diseases*: Hepatitis B and C, Mycoplasma.
- *Neoplastic diseases*: Lymphoma, leukemia, myeloma, Waldenström's macroglobulinemia, carcinoid syndrome, paraneoplastic disorders.
- *Environmental factors*: Vibration injury, vinyl chloride exposure, frostbite.
- *Endocrine disorders*: Acromegaly, myxedema, pheochromocytoma.
- *Hematologic diseases*: Paroxysmal nocturnal hemoglobinuria, polycythemia, cryoglobulinemia.
- *Drugs*: Oral contraceptives, ergot alkaloids, nicotine, cocaine, bromocriptine, sympathomimetics.

Pathophysiology

- Various abnormalities have been found in the vessels of patients with Raynaud's syndrome. These include endothelial dysfunction, deficiency of vasodilators such as nitric oxide, calcitonin gene-related peptide, and increase in vasoconstrictors such as endothelin-1, neuropeptide Y and thromboxane A2. Various neural abnormalities leading to an exaggerated vasospasm have also been documented.

Clinical Features

- Females are affected more commonly than males.
- Acral areas such as digits of the fingers are affected commonly, but toes, nose, and ears are affected occasionally.
- Affected areas show color changes usually in the order of white (pallor), blue (cyanosis), and red (hyperemia). Pallor is due to vasospasm. Cyanosis is due to reduction of blood flow. Red color is due to compensatory increase in blood flow (hyperemia). These color changes are usually transient but may rarely lead to local ischemia and gangrene. Numbness and pain in the affected areas may be present.
- There may be signs and symptoms of an underlying disorder (such as connective tissue disease).

Investigations

- Routine blood tests.
- Antinuclear antibody (ANA) and rheumatoid factor—may be positive in autoimmune diseases.
- Hepatitis panel: Positive for B or C infection in many patients with cryoglobulinemia.
- Other tests as per the suspected underlying disease.

Treatment

- *General measures*: These include reassurance, application of warmth to affected areas, stopping of any offending drugs. Patient should avoid cold environment.
- Vasodilators such as calcium channel blockers are useful as they prevent vasospasm. Nifedipine is most commonly used. Other drugs such as nicardipine, amlodipine, or diltiazem can also be used. Transdermal nitroglycerin can be added in severe cases.

- Parenteral prostaglandins such as prostaglandin E1 (PGE1), prostacyclin (PGI2), and iloprost (a PGI2 analog) have been shown to be of benefit in severe attacks causing digital ischemia.
- Cervical sympathectomy is useful for patients with recurrent attacks. It is more useful in patients with primary Raynaud's syndrome. Localized microsurgical digital sympathectomy has been gaining support as an alternative to cervical sympathectomy.
- Any underlying disorder should be treated.

Q. Discuss the etiology, pathogenesis, clinical features, diagnosis, and treatment of systemic sclerosis (scleroderma, CREST syndrome).

- Systemic sclerosis (previously called 'scleroderma') is a multisystem connective tissue disorder affecting the skin, internal organs and vasculature.
- Thickened skin (scleroderma) is the hallmark of this disease.
- It is more common in females (4 : 1 female : male ratio) and the peak age of onset is in the fourth and fifth decades.
- It is subdivided into diffuse cutaneous systemic sclerosis (DCSS) and limited cutaneous systemic sclerosis (LCSS). LCSS may have features of 'CREST' syndrome (calcinosis, Raynaud's, esophageal involvement, sclerodactyly, telangiectasia).

Etiology and Pathogenesis

- The exact etiology is unknown.
- Many environmental factors such as exposure to silica dust, vinyl chloride, hypoxy resins and trichloroethylene have been suspected to play a role in the causation of the disease.
- There is infiltration of skin by T-lymphocytes and abnormal fibroblast activation leading to excess collagen formation and thickening of skin (sclerodactyly). Fibrosis can happen in any organ leading to organ damage and functional impairment. Vessel wall inflammation and intimal thickening leads to narrowing of blood vessels.
- Systemic sclerosis can overlap with other autoimmune rheumatic disorders, e.g. sclerodermatomyositis (tight skin and muscle weakness indistinguishable from polymyositis) and mixed connective tissue disease.

Clinical Features

Skin Features

- Raynaud's phenomenon is seen in almost all patients and may precede other clinical features.
- Edematous swelling and erythema of the skin may precede skin thickening.
- Thickening and hardening of the skin. The skin of fingers, hands and face is first affected. Skin becomes taut and shiny. Skin creases disappear. Thickening of facial skin results in mask-like facies and microstomia.
- Skin involvement restricted to sites distal to the elbow or knee (apart from the face) is classified as 'limited cutaneous disease' or CREST syndrome. Involvement proximal to the knee and elbow and on the trunk is classified as 'diffuse cutaneous disease'.

Musculoskeletal Features

- Arthralgia
- Morning stiffness
- Tenosynovitis
- Myositis

Gastrointestinal Features

- Smooth muscle atrophy and fibrosis in the esophagus lead to esophageal reflux, dysphagia and odynophagia (painful dysphagia).
- Involvement of the stomach causes early satiety and occasionally outlet obstruction.
- Vascular ectasia in the stomach ("watermelon stomach") is frequent, and may cause recurrent gastrointestinal bleeding and anemia.
- Small and large bowel involvement may lead to malabsorption due to bacterial overgrowth, bloating, pain or constipation and pseudo-obstruction.

Pulmonary Features

- Interstitial lung disease.
- Pulmonary hypertension leading to progressive dyspnea, right heart failure and angina.
- Increase in the incidence of lung cancer.

Cardiac Features

- Right heart failure and angina due to pulmonary hypertension.
- Pericarditis
- Myocardial fibrosis
- Arrhythmias

Renal Features

- Proteinuria.
- Scleroderma renal crisis—this is a life-threatening renal disease and is more frequent in patients with DCSS. It is characterized by acute onset of renal failure and malignant hypertension.

Neurological Features

- Cranial, entrapment, peripheral, and autonomic neuropathies.

- CNS involvement, including headache, seizures, stroke, vascular disease, radiculopathy, and myelopathy.

Genitourinary Features

- Erectile dysfunction in men.
- Decreased vaginal lubrication or constriction of the vaginal introitus in women leading to dyspareunia.

Diagnosis

- Systemic sclerosis is mainly a clinical diagnosis based on the presence of typical skin thickening and hardening (sclerosis) along with the presence of extracutaneous features and characteristic autoantibodies.
- ESR is elevated. Anemia may be present.
- Skin biopsy—is usually not essential for confirmation of the diagnosis. However, skin biopsy is suggested if the diagnosis is in doubt. It is also helpful to differentiate from other causes of skin thickening.
- Autoantibodies—presence of many autoantibodies support the diagnosis of systemic sclerosis. These include anti-centromere, anti-topoisomerase-I (Scl-70), anti-RNA polymerase, or U3-RNP antibodies. ANA with a nucleolar staining pattern is frequently present.
- X-ray and CT scan chest if there is suspicion of ILD.
- Echocardiogram to rule out pulmonary hypertension and cardiac involvement.
- RFT and urine analysis to rule out renal damage.

Management

- Regular monitoring of BP, renal function tests and blood counts.
- Intravenous cyclophosphamide has been shown to slow the progression of the disease, but the drug has significant side effects.
- Corticosteroids and immunosuppressive agents are indicated in patients with myositis or interstitial lung disease.
- Raynaud's phenomenon—avoidance of cold exposure and use of vasodilators such as calcium channel blockers (nifedipine, amlodipine) or angiotensin II receptor blockers (e.g. valsartan) may be helpful. Sympathectomy may be tried in patients who do not respond to medical therapy.
- Esophageal dysmotility and acid reflux—this can be improved by proton pump inhibitors, and prokinetic agents such as erythromycin, itopride, etc.
- Infection of ulcerated skin should be treated with prompt antibiotic therapy.
- For severe digital ischemia, intermittent infusions of epoprostenol may be helpful.

Q. Sarcoidosis.

Definition

- Sarcoidosis is a chronic, systemic disease of unknown etiology characterized by the presence of non-caseating granulomas in one or more organ systems.
- Although it is a systemic disease, lungs and the lymph nodes in the mediastinum and hilar regions are affected more commonly.
- The clinical picture can vary from asymptomatic to multi-organ failure.

Epidemiology

- Sarcoidosis has worldwide distribution, but more common in Northern Europe, North America, and Japan. It mainly affects whites. It is less common in Asian countries like China, Africa, India, and Russia.
- Most patients present between 20 and 40 years of age. Women are affected more often than men.
- It occurs more commonly in nonsmokers unlike other lung diseases which occur in smokers.

Etiology

- Exact cause of sarcoidosis is unknown. Available evidence implicates exaggerated cellular immune response as the etiological factor. Immunological response is triggered by some antigens. Genetic factors may also make a person more susceptible.
- A variety of exogenous agents, both infectious and non-infectious, have been hypothesized as possible causes of sarcoidosis. It has been suggested that an exogenous agent induces immunologic sensitization, by acting as a "hapten" that binds to peptides or alters major histocompatibility complex molecules. Some of the agents implicated are *Mycobacterium tuberculosis*, atypical mycobacteria, viruses, fungi, protozoa, pine pollen, etc. Beryllium can produce an identical illness in human beings. Recent workers have found evidence of mycobacterial DNA in sarcoid tissue.
- Recurrence of disease can occur in the transplanted lung of patients who receive a transplant for end-stage sarcoidosis. In addition, sarcoidosis has been reported to develop in the transplant recipient of tissue from a donor with sarcoidosis.

Pathogenesis

- The unknown antigen triggers a cell-mediated immune response. The first manifestation of sarcoidosis is an accumulation CD4+ T-lymphocytes and mononuclear phagocytes in affected organs. This inflammatory process is followed by the formation of granulomas, aggregation

of macrophages, epithelioid cells, and multinucleated giant cells. Organ dysfunction results from the granulomas and accumulated inflammatory cells distorting the architecture of the affected tissue. Chronic inflammation in the organs may lead to fibrosis and permanent damage.

- Hypercalcemia may occur because vitamin D analogs are produced by activated macrophages. Nephrolithiasis and nephrocalcinosis may occur, sometimes leading to chronic kidney disease.

Clinical Manifestations

- Sarcoidosis is notable for its protean manifestations and variable course. Any organ can be affected, but the respiratory system is most commonly affected. In addition to the symptoms attributable to the involved organ systems, systemic symptoms like fever, malaise, weight loss and joint pains can also occur.
- *Respiratory system*: 90% of patients with sarcoidosis have pulmonary involvement on chest X-ray. Upper lobes tend to be more affected than the lower lobes. Pleura and airways can also be affected. Severe disease may lead to irreversible fibrosis and honeycombing. Patients usually present with respiratory symptoms, such as dyspnea and cough. Crepitations may be heard on auscultation of lungs. Extrapulmonary disease can occur without concomitant pulmonary involvement but rare.
- *Hematologic*: Lymphocytopenia, anemia of chronic disease, pancytopenia due to granulomatous infiltration of bone marrow, splenic sequestration causing thrombocytopenia, leukopenia.
- *CVS*: Involvement results in conduction defects, arrhythmias, and heart failure.
- *Nervous system*: Manifestations include facial nerve palsy (most common manifestation), seizures, meningitis, peripheral neuropathy, and psychiatric symptoms. Virtually any part of the nervous system can be involved
- *GIT*: Hepatosplenomegaly is common. Parotid involvement leads to bilateral swelling. Pancreas also can be involved.
- *Skin*: Cutaneous manifestations include papules, plaques, nodules, erythema nodosum, infiltration of old scars, and lupus pernio.
- *Eye*: Involvement takes the form of anterior or posterior uveitis, conjunctival involvement, and papilledema. Heerfordt's syndrome or uveoparotid fever, is a form of sarcoidosis in which anterior uveitis is accompanied by parotid gland enlargement and often fever and facial palsy.
- *Musculoskeletal system*: Effusion into joints, myalgia and arthralgia may occur.
- Endocrine system: Diabetes insipidus may result from hypothalamus lesions. Diabetes mellitus can occur due to pancreas involvement. Hypopituitarism and hypothyroidism have also been recorded.

Investigations

- Elevation of angiotensin-converting enzyme (ACE) and calcium can occur. Hypercalcemia may be due to elevated levels of 1, 25-dihydroxyvitamin D produced by macrophages within the granulomas. Elevation in ACE is believed to be due to production of the enzyme by epithelioid cells and macrophages within the granulomas.
- The diagnosis of sarcoidosis is confirmed by the finding of non-caseating granulomas in the affected organs, with appropriate additional investigations to exclude other causes of granulomas. Flexible bronchoscopy with transbronchial lung biopsy is particularly useful.
- Kveim test is done by intradermal injection of a validated antigen. Formation of a typical granuloma is highly specific and sensitive. Tuberculin test is usually negative in sarcoidosis.
- Chest X-ray shows hilar lymphadenopathy, and involvement of the pulmonary parenchyma. Interstitial, alveolar and nodular pattern opacities may also be seen.
- High resolution CT scan of chest shows mediastinal lymphadenopathy and opacities better than chest X-ray.
- Gallium scanning may demonstrate uptake of this isotope in regions involved with granulomatous inflammation but not routinely recommended.

Natural History and Prognosis

- The natural history of sarcoidosis is variable, ranging from spontaneous resolution to progressive disease. Patients with progressive disease can become disabled from significant organ system involvement, particularly respiratory failure from interstitial lung disease.

Treatment

- Because sarcoidosis has a variable natural course, it is often difficult to decide whether and when therapy should be started. Serial evaluation can assess whether the disease is improving spontaneously. Whenever there is significant ocular, myocardial, or neurologic involvement, treatment is started early. Intrathoracic lymph node involvement does not require treatment, but lung parenchymal involvement requires treatment.
- Corticosteroids are the drugs of choice to suppress inflammation. Prednisolone is started at a dose of 0.5 mg to 1 mg/kg/day, and continued for several weeks and then tapered to a lower dose which is continued for 6–12 months. The optimum duration of therapy is not

known and needs to be individualized based on response. Premature discontinuation of therapy may lead to recurrence of disease. Alternative agents include methotrexate (7.5 to 15 mg per week), or other immunosuppressive or cytotoxic agents such as cyclophosphamide and azathioprine.

- Hydroxychloroquine has been used for serious and disfiguring cutaneous sarcoidosis. Dose is 250 to 750 mg/day for 6 to 9 months.
- Tumor necrosis factor (TNF) receptor antagonists such as etanercept and infliximab have shown benefit in some trials.
- In patients with severe, end-stage pulmonary disease, lung transplantation is an important option, but the disease may affect the transplanted lungs also.

Q. What are the idiopathic inflammatory myopathies?

Q. Discuss the etiology, classification, clinical features, diagnosis, and management of polymyositis-dermatomyositis.

- Idiopathic inflammatory myopathies are rare connective tissue disorders characterized by the presence of muscle inflammation (myositis) and weakness.
- These include polymyositis, dermatomyositis and inclusion body myositis.
- The term polymyositis is used when the condition spares the skin and the term dermatomyositis is used when the condition involves the skin.
- They are more common in females (2 : 1 ratio).

Etiology

- The exact etiology is unknown.
- Genetic factors may play a role.
- Other connective tissue diseases such as SLE or vasculitis can cause myositis.
- They may be associated with malignancy.

Classification

- Primary idiopathic polymyositis can occur at any age and does not involve the skin.
- Primary idiopathic dermatomyositis is similar to primary idiopathic polymyositis but also involves the skin.
- Polymyositis or dermatomyositis associated with cancer usually occurs in older adults.
- Childhood dermatomyositis can be associated with systemic vasculitis.
- Polymyositis or dermatomyositis can occur with an associated disorder such as progressive systemic sclerosis, mixed connective tissue disease, RA, SLE, or sarcoidosis.

Clinical Features

Polymyositis

- The onset is usually between 40 and 60 years of age and is insidious.
- The most common presentation is with symmetrical proximal muscle weakness, usually affecting the lower limbs first. There is difficulty in getting from sitting position and climbing stairs. Muscle pain may be present. Respiratory or pharyngeal muscle involvement leads to dyspnea and aspiration.
- Systemic features such as fever, weight loss and fatigue may be present.
- Interstitial lung disease causes progressive dyspnea and dry cough.

Dermatomyositis

- Muscle manifestations are similar to polymyositis.
- Skin manifestations are as follows:
  - Gottron's papules are scaly erythematous plaques or papules occurring over the extensor surfaces of interphalangeal joints.
  - Heliotrope rash is a violaceous eruption on the upper eyelids, often accompanied by eyelid edema.
  - Shawl sign and V sign—shawl sign is an erythematous lesion occurring over the chest and shoulders (shawl distribution) or in a V-shaped distribution over the anterior neck and chest.
  - Periungual nail-fold capillaries are often abnormal.
  - Mechanic's hands—this is roughening and cracking of the skin of the tips and lateral aspects of the fingers resembling those of a manual laborer.
- Systemic features such as fever, weight loss and fatigue may be present.

Diagnosis

- These conditions should be suspected when there is proximal muscle weakness without neuropathy, and there is evidence of systemic disease.
- Creatine kinase (CK) is usually elevated.
- Electromyography (EMG) to confirm myopathy and exclude neuropathy.
- Muscle biopsy shows features of inflammation, necrosis, and regeneration. MRI is useful to identify areas of abnormal muscle for biopsy.
- CT scans of chest/abdomen/pelvis, and mammography to rule out any underlying malignancy.

Management

- *Steroids:* Oral steroids (e.g. prednisolone 40–60 mg daily) are the mainstay of treatment. Intravenous steroids

(methylprednisolone 1 g daily for 3 days) may be required for severe weakness or respiratory or pharyngeal weakness. Steroids should be tapered slowly to a maintenance dose of 5 to 7.5 mg per day.

- *Immunosuppressive agents*: These are required if there is inadequate response to steroids. Azathioprine and methotrexate are the first choice and cyclosporin, cyclophosphamide, tacrolimus and intravenous immunoglobulin are alternatives.
- *General measures*: Physiotherapy, avoidance of sunlight, prevention of opportunistic infections, etc.

Q. Inclusion body myositis.

- This is the most common disease of muscle in patients over the age of 50.
- It affects men more often than women.
- Distal muscle weakness is more common than proximal weakness. Other clinical features are similar to polymyositis.
- Investigation findings are similar to polymyositis and dermatomyositis. However, muscle biopsy shows characteristic rimmed vacuoles and filamentous inclusions in the nucleus and cytoplasm of muscle fibres (hence called inclusion body myositis).
- Treatment is with steroids and immunosuppressive agents. However, the response is poor.

Q. Discuss the clinical features, investigations and management of Sjögren's syndrome.

Q. Keratoconjunctivitis sicca.

- Sjögren's syndrome (SS) is an autoimmune disorder of unknown etiology characterized by lymphocytic infiltration of exocrine glands, leading to glandular fibrosis and exocrine failure. Salivary and lacrimal glands are commonly involved.
- Sjögren's syndrome can be classified into primary SS or secondary SS. Primary SS is not associated with other diseases. Secondary SS occurs as a complication of other rheumatic disorders such as rheumatoid arthritis, SLE, polymyositis or scleroderma.

Clinical Features

- Patients are generally old (mean age 50 years) and more than 90% are women.

Exocrine Gland Involvement

- Dry eyes (keratoconjunctivitis sicca) occur due to lacrimal gland involvement. The ocular symptoms of dry eyes are irritation, grittiness, and a foreign body sensation. Conjunctivitis and blepharitis are frequent but keratitis can also occur.
- Dry mouth (xerostomia) occurs due to salivary gland involvement. Salivary glands may be enlarged. Decreased salivary secretion leads to difficulty swallowing dry food without water. Oral dryness leads to increased risk of dental caries and periodontal disease.
- Vaginal dryness can lead to dyspareunia.
- Exocrine gland involvement in the skin may lead to xerosis.

Extraglandular Features

- *Musculoskeletal system*: Non-erosive arthritis.
- *Nervous system*: Peripheral neuropathy.
- *Kidneys*: Glomerulonephritis, renal tubular acidosis.
- *Heart*: Pericarditis.
- *RS*: Interstitial lung disease.
- *GIT*: Dysphagia.
- Lymphadenopathy.
- Thyroid—hypothyroidism.
- *Vascular*: Vasculitis, Raynaud's phenomenon.
- Increased incidence of lymphoma.
- Low-grade fever, fatigue.

Investigations

- Anemia, leukopenia, thrombocytopenia.
- Elevated ESR.
- Cryoglobulinemia.
- *Autoantibodies*: ANA and rheumatoid factor are usually positive. Other antibodies which can be present are SS-A (anti-Ro), SS-B (anti-La) and gastric parietal cell antibodies.
- *Schirmer test* is done by placing absorbent paper strips in the lower lacrimal sac for 5 minutes. Less than 5 mm of wetting is abnormal.
- *Biopsy*: Diagnosis can be confirmed by finding lymphocytic infiltrate in the minor salivary glands on lip biopsy.

Management

- Artificial lubrication is the mainstay of symptomatic treatment. Artificial tears such as hypromellose drops can be used for the eyes. Occlusion of the lacrimal ducts can increase the tear content of the eyes. Artificial saliva and oral gels can be tried for xerostomia. Stimulation of saliva flow by sugar-free chewing gum or lozenges may be helpful. Oral hygiene is important to prevent caries and gum problems. Vaginal dryness is treated with lubricants such as K-Y jelly.
- Extra-glandular manifestations can be treated by steroids and immunosuppressive drugs such as azathioprine. Immunosuppression has no effect on sicca symptoms.

Q. Define vasculitis. Discuss the classification, clinical features, investigations and management of vasculitis (systemic vasculitis).

- Vasculitis is a clinicopathologic process characterized by inflammation of and damage to blood vessels. Vasculitis can affect any blood vessel—arteries, arterioles, veins, venules, or capillaries.
- Vasculitis may be primary or secondary. Primary vasculitis mainly affects blood vessels and has no known cause. Secondary vasculitis may be triggered by an infection, a drug, or a toxin or may occur as part of another inflammatory disorder or cancer.
- Exact etiology is unknown, although geographic, environmental and genetic factors may play a role.
- Vasculitis may lead to blockage of the involved blood vessels and this leads to ischemia of the tissues supplied by the vessel.

Classification

- Vasculitis has been classified based on the predominant size of blood vessels affected. However, there is often substantial overlap.

Large vessel vasculitis
- Giant cell arteritis
- Takayasu's arteritis

Medium vessel vasculitis
- Polyarteritis nodosa (PAN)
- Kawasaki disease

Small vessel vasculitis
- Microscopic polyangiitis
- Wegener's granulomatosis
- Churg-Strauss syndrome
- Henoch-Schönlein purpura
- Mixed essential cryoglobulinemia
- Hypersensitivity vasculitis (due to drugs, etc.)
- Vasculitis secondary to connective tissue disorders (SLE, RA)
- Vasculitis secondary to viral infection (hepatitis B and C)

Clinical Features

- Clinical features are produced due to a combination of local tissue ischemia caused by vessel block and the systemic inflammation.
- Systemic vasculitis should be suspected in a patient with fever, weight loss, fatigue, multisystem involvement, rashes, raised inflammatory markers and abnormal urinalysis.

Systemic
- Fever, night sweats, weight loss.

Musculoskeletal
- Arthralgia, myalgia.

Ear, nose and throat
- Epistaxis, recurrent sinusitis, deafness.

Ophthalmologic
- Vision loss in giant cell arteritis (temporal arteritis)

Respiratory
- Cough, hemoptysis, wheezing.

Gastrointestinal
- Mouth ulcers, diarrhea, abdominal pain (due to mucosal inflammation or enteric ischemia).

Neurological
- Mononeuritis multiplex, polyneuropathy, radiculopathy, stroke.

Renal
- Hematuria, proteinuria.

Rashes
- Palpable purpura, pulp infarcts, ulceration, livedo reticularis.

Investigations

- ESR and CRP are elevated.
- Routine biochemistry.
- Urinalysis (may show proteinuria and hematuria).
- Autoantibodies (ANA, antineutrophil cytoplasmic antibodies (ANCA), RA factor, cryoglobulins).
- Hepatitis B and C serology.
- HIV-ELISA.
- *Biopsy*: Biopsy from an involved site such as skin, nasal mucosa can show vessel wall inflammation.
- Visceral angiography to detect microaneurysms (e.g. classical polyarteritis nodosa) is useful if biopsy is difficult to take from involved tissue.

Management

- Management depends on the nature and severity of the vasculitis.
- Hypersensitivity vasculitis may respond to withdrawal of the offending drug, antihistamines and a short-course of steroids.
- Oral steroids plus cytotoxic (cyclophosphamide) drugs are required for severe systemic vasculitis with multiorgan involvement.
- Azathioprine and methotrexate can be used in less severe forms of vasculitis and as maintenance therapy after remission has been induced by cyclophosphamide.

Q. Giant cell arteritis (temporal arteritis).

- Temporal arteritis (giant cell arteritis) is a systemic inflammatory vasculitis occurring commonly in older individuals.
- Giant cell arterirts (GCA) commonly affects the superficial temporal arteries and its branches—hence the

term temporal arteritis. In addition, GCA also affects the ophthalmic, occipital, vertebral, posterior ciliary, and proximal vertebral arteries. It can cause permanent blindness by causing occlusion of the posterior ciliary or central retinal arteries.

Pathophysiology

- Basically there is inflammation of the vessel wall leading to edema of the vessel wall and occlusion. Biopsy shows inflammatory cell infiltration into all three layers of the vessel wall.

Clinical Features

- GCA may begin with constitutional symptoms such as fever, anorexia, malaise, and myalgia.
- Headache, orbital or frontotemporal, dull and constant in nature, aggravated by cold temperatures.
- Jaw claudication noted as fatigue or discomfort of the jaw muscles during chewing. Jaw claudication is almost pathognomonic of temporal arteritis, and it is a result of ischemia of the maxillary artery supplying the masseter muscles.
- *Ophthalmologic symptoms*: Unilateral visual blurring or vision loss, or occasionally diplopia. A partial field defect may progress to complete blindness over days. Fundus examination may show pale or swollen optic disc, retinal splinter hemorrhages or a pale retina, and cherry-red spot (i.e. central retinal artery infarction).
- Tenderness may be present on the scalp and over the temporal artery.

Investigations

- ESR is the best screening test and is usually markedly elevated (i.e. >50). A normal ESR does not rule out GCA.
- CRP is also elevated.
- Temporal artery biopsy is required for definitive diagnosis.
- Color duplex ultrasonography of the temporal artery has emerged as a promising alternative or complement to biopsy.

Treatment

- Treatment with steroids should be initiated promptly on suspecting temporal arteritis. Otherwise, permanent visual loss can occur. Intravenous methylprednisolone (500 to 1000 mg every 12 hours for 48 hours) followed by oral prednisone (80 to 100 mg/day for 14 to 21 days), with a gradual taper over 12 to 24 months.
- Alternative immunosuppressant agents (e.g. cyclosporin, azathioprine, methotrexate) may be started later in the course of treatment. They are useful as steroid-sparing agents in patients who require prolonged treatment with high dose steroids.

Q. Takayasu arteritis (pulseless disease; occlusive thromboaortopathy; aortic arch syndrome).

- Takayasu arteritis is a large vessel vasculitis. It mainly affects aorta, carotid, ulnar, brachial, radial and axillary arteries.
- The etiology is unknown.
- It is more common in women (female : male ratio 8 : 1) between 25 and 30 years.
- Clinical features are claudication with systemic symptoms (fever, arthralgia and weight loss). There may be absent pulses and bruits.
- Investigations show high ESR and anemia. Angiography shows coarctation, occlusion and aneurysmal dilatation.
- Treatment is with steroids (oral prednisolone). Additional therapy with methotrexate or cyclophosphamide is usually required.

Q. Discuss the etiology, clinical features, diagnosis, and management of classical polyarteritis nodosa (PAN).

- Classical PAN is a necrotizing vasculitis which mainly affects medium-sized arteries.
- It affects all age groups, with a peak incidence in the fourth and fifth decades.
- It is more common in males (male : female ratio of 2 : 1).

Etiology

- Exact etiology is unknown.
- Hepatitis B and C can be associated with PAN.

Clinical Features

- *Systemic symptoms*: Fever, weight loss, arthralgia and myalgia.
- *Skin lesions*: Ulceration, livedo reticularis, infarction and gangrene of fingers or toes.
- *Nervous system*: Involvement of vasa nervosum (vessels supplying nerves) leads to neuropathy which commonly presents as mononeuritis multiplex. CNS involvement can present with headache, seizures and ischemic stroke.
- *Cardiac*: Involvement of coronary arteries can cause angina and heart failure.
- *Gastrointestinal*: Vasculitis of the liver or gallbladder causes right upper quadrant pain. Vasculitis of mesenteric arteries causes abdominal pain, bloody diarrhea, malabsorption, intestinal perforation, and acute abdomen.

- *Renal*: Hypertension, oliguria, uremia. Renal failure may occur due to multiple renal infarctions.
- *Genital*: Orchitis with testicular pain and tenderness can occur.

Diagnosis

- Raised ESR and anemia.
- Angiography shows multiple aneurysms and smooth narrowing of medium-sized arteries such as mesenteric, hepatic or renal arteries.
- Testing for hepatitis B and C.
- Autoantibody testing to rule out other connective tissue diseases which can cause vasculitis. These are ANCA, rheumatoid factor, anticyclic citrullinated peptides (CCP), ANA, complement levels, anti-Smith, anti-Ro/SSA, anti-La/SSB, and anti-RNP, etc.
- Tissue biopsy (muscle or sural nerve) may show vessel wall inflammation.

Treatment

- Steroids and cyclophosphamide to control vessel wall inflammation.
- Treat the underlying cause such as hepatitis B or C infection.

Q. Microscopic polyangiitis.

- Microscopic polyangiitis is a necrotizing vasculitis affecting microscopic vessels such as capillaries, venules, or arterioles.
- Other diseases causing small vessel vasculitis are granulomatosis with polyangiitis (Wegener granulomatosis), and Churg-Strauss syndrome. All these three diseases cause small vessel vasculitis related to antineutrophil cytoplasmic antibodies (ANCAs) and are characterized by a paucity of immune deposits. However, Wegener's granulomatosis is characterized by granuloma formation and upper respiratory tract involvement which is absent in microscopic polyangiitis.
- Also note that microscopic polyangiitis differs from PAN in that PAN does not involve small vessels such as capillaries, venules, or arterioles.

Clinical Features

- The mean age of onset is ~57 years, and males are more affected than females.
- Systemic symptoms include fever, weight loss, arthralgia and myalgia.
- Glomerulonephritis occurs in majority of patients and can be rapidly progressive, leading to renal failure.
- Pulmonary capillaritis can cause alveolar hemorrhage.
- Other manifestations include neuropathy, gastrointestinal tract and cutaneous vasculitis.

Investigations

- Elevated ESR, anemia, leukocytosis, and thrombocytosis.
- p-ANCA is positive in majority of patients.
- Biopsy of the involved tissue shows vessel wall inflammation.

Treatment

- Life-threatening disease should be treated with intravenous methylprednisolone and cyclophosphamide.
- Maintenance treatment is with oral steroids and oral cyclophosphamide.
- Plasma exchange may help in ANCA-positive patients with acute renal failure.

Q. Granulomatosis with polyangiitis (Wegener's granulomatosis).

- Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) is a type of small vessel vasculitis characterized by necrotizing granulomatous vasculitis which predominantly affects respiratory tract and kidneys.

Clinical Features

- Most common presentation is with upper airway involvement which may produce epistaxis, nasal crusting and sinusitis, mucosal ulceration and deafness due to serous otitis media. Untreated nasal disease leads to destruction of bone and cartilage.
- Pulmonary involvement may produce cough, dyspnea and hemoptysis.
- Renal involvement produces acute glomerulonephritis, hematuria, and proteinuria.
- Proptosis may be present due to inflammation of the retro-orbital tissue.

Investigations

- *Chest X-ray*: Migratory pulmonary infiltrates and nodules.
- c-ANCA (cytoplasmic antineutrophil cytoplasmic antibodies) is usually positive.
- *Biopsy of the involved tissue*: Lung biopsy may show characteristic necrotizing granulomatous vasculitis. Renal biopsy may show necrotizing crescentic glomerulonephritis without immunoglobulin deposition (pauci-immune).

Treatment

- Same as microscopic polyangiitis.

Q. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

- Eosinophilic granulomatosis with polyangiitis (formerly called Churg-Strauss syndrome) is a systemic small and medium vessel vasculitis, characterized by extravascular granulomas, eosinophilia, and tissue infiltration by eosinophils.

Etiology

- Exact cause is unknown. It is probably due to an allergic or autoimmune reaction to an environmental agent or drug.

Clinical Features

- The most common organ involved is lung, followed by skin. However, any organ can get affected.
- Clinical manifestations occur in several sequential phases:
  - Prodromal phase—it is characterized by atopic disease, allergic rhinitis, and asthma.
  - Eosinophilic phase—there is peripheral blood eosinophilia and eosinophilic infiltration of many organs, especially the lung and gastrointestinal tract.
  - Vasculitic phase—there is life-threatening systemic vasculitis of the small and medium vessels. Vasculitis phase may be associated with systemic symptoms such as fever, weight loss, and fatigue.
- Skin manifestations include purpura or nodules.
- Pulmonary infiltrates and pleural or pericardial effusions due to serositis may be present.
- Abdominal symptoms may be present due to mesenteric vasculitis.

Investigations

- Elevated ESR and CRP.
- Peripheral blood eosinophilia (>10%).
- Urine shows RBC casts and proteinuria.
- Chest X-ray may show infiltrates and pleural or pericardial effusions.
- c-ANCA or p-ANCA may be positive.
- Biopsy of the affected tissue shows vasculitis with extravascular eosinophils.

Treatment

- Same as microscopic polyangiitis.

Q. Henoch-Schönlein purpura (HSP) or anaphylactoid purpura.

- HSP is a small vessel vasculitis which mainly occurs in children and young adults.
- HSP is self-limited in majority of cases.

Clinical Features

- The classic tetrad of HSP includes: Palpable purpura, arthritis/arthralgia, abdominal pain and renal disease. The onset usually follows an upper respiratory tract infection.
- Palpable purpurae are due to vasculitis involving skin blood vessels and mainly found over the buttocks and lower legs.
- Abdominal symptoms include colicky pain and bleeding.
- Arthritis/arthralgia usually involves knee or ankle.
- Renal involvement produces hematuria, proteinuria and in some cases renal failure.

Investigations

- ESR and CRP are elevated.
- Serum IgA levels may be elevated.
- Abnormal renal function tests and proteinuria.
- Biopsy of the skin (purpuric spot) or kidney may show IgA deposition within and around blood vessel walls.

Treatment

- Steroids are effective for gastrointestinal and joint involvement.
- Renal involvement requires treatment with both pulse IV steroids and immunosuppressants (cyclophosphamide, azathioprine).
- Plasmapheresis may be effective in delaying the progression of kidney disease.

Q. Behçet's disease.

- Behçet's disease is a chronic, relapsing, autoimmune disease characterized by triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis.

Etiology

- Exact cause is unknown.
- Immunologic (including autoimmune) and viral or bacterial triggers have been suggested, and HLA-B51 is associated with some cases.

Clinical Features

- Behçet's disease involves multiple systems. The most common feature is the presence of recurrent muco-cutaneous ulcers.
- *Oral ulcerations*—most patients have recurrent oral aphthous ulcerations. The ulcers are painful and range in size from a few millimeters to two centimeters. These ulcers heal spontaneously but recur again and again.
- *Genital ulcers*—these are similar to oral ulcers and are painful. They commonly occur on the scrotum and vulva.

- *Skin leisons*—include acneiform lesions, papulo-vesiculopustular eruptions, nodules, erythema nodosum, superficial thrombophlebitis, and pyoderma gangrenosum. Pathergy refers to an erythematous papular or pustular response to local skin injury. It is defined as a greater than 5 mm lesion that appears 24 to 48 hours after skin prick by a needle.
- *Ocular disease*—uveitis is the main feature. It is bilateral and episodic. Other manifestations are retinal vasculitis, vascular occlusion, and optic neuritis. All these may lead to blindness if untreated.
- *Vascular disease*—Behçet's disease can involve blood vessels of all sizes. Most clinical manifestations of Behçet's disease are believed to be due to vasculitis.
- Other features are arthritis, meningoencephalitis, epididymitis, intestinal ulcerations, renal, cardiac and lung involvement.

Diagnosis

Criteria for the diagnosis of Behçet's disease

- Recurrent oral ulceration—aphthous (idiopathic) ulceration, observed by physician or patient, with at least three episodes in any 12 month.

Plus two of:

- Recurrent genital ulceration
- Eye lesions—anterior or posterior uveitis or retinal vasculitis
- Skin lesions—erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules
- Positive pathergy test

Treatment

- Oral ulcers are treated with topical steroid preparations. Thalidomide is very effective for resistant oral and genital ulceration but is teratogenic and neurotoxic.
- Colchicine is effective for erythema nodosum and arthralgia.
- Systemic disease requires oral steroids with other immunosuppressive drugs.

Q. Fibromyalgia (myofascial pain syndrome; fibrositis; fibromyositis).

- Fibromyalgia is a chronic pain disorder of unknown etiology. It is a very common cause of multiple regional musculoskeletal pain and disability.
- It is more common in females and increases with age.

Etiology

- Exact etiology is unknown. Current evidence suggests fibromyalgia may be a centrally mediated disorder of pain sensitivity. Risk factors are psychosocial stresses such as divorce, marital disharmony, alcoholism in the family, assault, low income, etc. Reduced delta waves during NREM sleep have been found in patients with fibromyalgia. Delta wave sleep has restorative function.

Clinical Features

- Multiple regional pain, often focusing on the neck and back. Pain does not respond to analgesics and NSAIDs. Reduced threshold to pain perception and tolerance are present. Fatigability is another major problem. Other features are low mood, irritability, weepiness, swelling of hands and fingers, numbness and tingling of fingers, non-throbbing bifrontal headache.
- Examination of musculoskeletal and neurological system is normal. The main finding is hyperalgesia at tender sites.

Differential Diagnosis

- Chronic fatigue syndrome can cause similar generalized myalgias and fatigue and laboratory test results are typically normal.
- Polymyalgia rheumatica can cause generalized myalgias. However, it usually affects older adults, tends to affect proximal muscles selectively, and ESR is high.

Management

- Involves education concerning the nature of the problem, pain control and improvement of sleep. Low-dose amitriptyline (10–75 mg at night) with or without fluoxetine may be useful.

Q. Polymyalgia rheumatica (PMR).

- Polymyalgia rheumatica is a rheumatic condition associated with muscle pain and stiffness and, an increased ESR.
- It is not a true vasculitis but there is a close association with giant cell arteritis. Polymyalgia rheumatica occurs in about 50% of patients with giant cell arteritis.
- People over 50 years of age are mainly affected. Women are affected more often than men (3 : 1 ratio).

Clinical Features

- Main features are subacute or chronic onset of muscle stiffness and pain in the shoulders, hip girdles, neck and torso in patients over the age of 50. There is marked early morning stiffness, often with night pain.
- Examination shows stiffness and restriction of active movements but passive movements are normal. There may be muscle tenderness but no muscle-wasting. If muscle wasting is there, then primary muscle or neurological disease should be suspected.

- Systemic features are weight loss, fatigue, and night sweats.

Investigations

- Elevated ESR and CRP.
- Normochromic, normocytic anemia.

Management

- Treatment is with steroids (prednisolone). There is dramatic response within 72 hours. If there is no response by 72 hours or an incomplete response by 7 days, then other conditions should be suspected.
- Most patients need steroids for an average of 12–18 months. Immunosuppressants such as methotrexate or azathioprine can be considered if steroids cannot be withdrawn at 2 years.

Q. Antineutrophil cytoplasmic antibodies (ANCAs).

- ANCAs are autoantibodies directed against certain proteins in the cytoplasm of neutrophils and monocytes. They are mainly of the IgG type.
- ANCA can be measured by two methods; indirect immunofluorescence assay and enzyme-linked immunosorbent assay (ELISA)
- There are two major types of ANCA: c-ANCA and p-ANCA. c-ANCA (cytoplasmic ANCA) refers to cytoplasmic staining pattern observed by immunofluorescence microscopy when serum antibodies bind to indicator neutrophils. p-ANCA (perinuclear ANCA) refers to perinuclear or nuclear staining pattern of the indicator neutrophils.

Significance

- ANCAs are positive in systemic vasculitis syndromes, particularly Wegener's granulomatosis and microscopic polyangiitis, and in patients with necrotizing and crescentic glomerulonephritis.
- ANCA can also be positive in non-vasculitic rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome, etc. Hence, ANCA positivity alone is not diagnostic of vasculitis.
- The levels of ANCA do not correlate with disease activity.

Q. Antinuclear antibodies (ANAs).

- ANAs are autoantibodies directed against various nuclear antigens.

Conditions Associated with Positive ANA

Systemic autoimmune diseases

- Systemic lupus erythematosus (SLE)
- Scleroderma
- Mixed connective tissue disease
- Polymyositis/dermatomyositis
- Rheumatoid arthritis
- Sjögren's syndrome

Specific organ autoimmune disease

- Hashimoto's thyroiditis
- Graves' disease
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Idiopathic pulmonary arterial hypertension

Infections

- Hepatitis C infection
- Subacute bacterial endocarditis
- Tuberculosis
- HIV infection

Significance

- ANAs are serologic hallmarks of patients with systemic autoimmune diseases. Testing for antinuclear antibodies (ANAs) is commonly used when evaluating patients who are suspected of having an autoimmune or connective tissue disorder.
- Very high concentrations of antibody (titre >1 : 640) should arouse suspicion of an autoimmune disorder even in a patient without any symptoms.
- ANA is also useful to monitor disease activity and to determine the specific type of disease.

Types of ANA

- Certain types of antinuclear antibodies are somewhat specific to certain diseases. The main types of ANA are as follows.
- *Antibodies to double-stranded DNA (anti-ds DNA)*—these are found in SLE and rheumatoid arthritis.
- *Antibodies to histone proteins*—these are found in SLE and drug-induced lupus.
- *Antibodies to chromatin*—these are especially prevalent in SLE patients with renal disease.

False Positive Tests

- The ANA test is said to be false positive when a person tests positive but does not have any other features of autoimmune disease. False positive result occurs often in women and elderly people. Drugs such as hydralazine, isoniazid, and procainamide can cause false positive results.

Q. Antiphospholipid syndrome (antiphospholipid antibody (APLA) syndrome).

- The antiphospholipid (AP) syndrome also known as antiphospholipid antibody (APLA) syndrome is characterized by antibodies directed against either phospholipids or plasma proteins bound to anionic phospholipids.
- These antiphospholipid antibodies include lupus anticoagulant (also known as lupus antibody) and anticardiolipin (aCL) antibody. The antibodies in AP syndrome have prothrombotic effect and also have action on vascular tone causing the clinical manifestations of AP syndrome.

Etiology

- AP syndrome is an autoimmune disorder of unknown cause. However following conditions can be associated with AP syndrome.
  - *Autoimmune diseases*: SLE, Sjögren's syndrome, rheumatoid arthritis.
  - *Infections*: Syphilis, hepatitis C infection, HIV infection.
  - *Drugs*: Procainamide, quinidine, propranolol, hydralazine, phenytoin, chlorpromazine.
  - *Genetic predisposition*: Relatives of persons with known AP syndrome are more likely to have AP syndrome.
  - *HLA associations*: Individuals who carry certain HLA genes DR7 and DR4 have increased risk of developing AP syndrome.

Clinical Features

- These patients may have a variety of clinical manifestations including venous and arterial thrombosis, recurrent fetal losses, neurologic events, and thrombocytopenia.
- *Thrombotic events*: Deep vein thrombosis and pulmonary embolism, ischemic stroke, peripheral and intra-abdominal vascular occlusion.
- *Obstetric complications*: Recurrent spontaneous abortions and fetal growth retardation, which probably are due to thrombosis of placental vessels.
- Catastrophic APS1 is the most severe form of APS with clinical evidence of multiple organ involvement developing over a short time with histopathological evidence of small vessel occlusions. It is a medical emergency with high mortality.

Diagnosis

- Diagnosis of antiphospholipid syndrome is based on a combination of clinical history and laboratory testing. APLS should be suspected if there is:
  - Occurrence of one or more otherwise unexplained thrombotic or thromboembolic events.
  - Recurrent abortions.
  - Unexplained thrombocytopenia or prolongation of a test of blood coagulation (e.g. PT or aPTT).
- Presence of lupus anticoagulant and anticardiolipin antibodies should be tested.

Treatment

Prophylactic Therapy to Prevent Thrombosis

- Prophylaxis is needed during surgery or hospitalization. Low-dose aspirin or clopidogrel can be used to prevent thrombotic events.

Patients with History of Thrombosis

- Intravenous heparin followed by warfarin should be used. International normalized ratio (INR) should be maintained between 2 and 3. Lifelong treatment may be required for patients with recurrent thrombotic events.

Pregnant Women with APS

- Treatment of antiphospholipid syndrome during pregnancy reduces the risks of pregnancy loss, pre-eclampsia, placental insufficiency, preterm birth, and thrombosis. Women with antiphospholipid syndrome and no history of thrombosis should receive heparin and low-dose aspirin during pregnancy and for six to eight weeks postpartum. Patients who require heparin administration throughout pregnancy should receive calcium and vitamin D supplementation to help avoid heparin-induced osteoporosis.
- Some studies have shown that aspirin alone is as efficacious as heparin plus aspirin.

Q. Lupus anticoagulant.

- The lupus anticoagulant (also known as lupus antibody) is an IgM or IgG immunoglobulin which binds to phospholipids and proteins associated with the cell membrane. Lupus anticoagulant is a misnomer as it is actually a prothrombotic agent. It produces a prolonged PTT by binding to the phospholipid used in the *in vitro* PTT assay; hence it is called lupus anticoagulant.

Etiology

- Lupus anticoagulant (LA) is seen in 20–45% of patients with systemic lupus erythematosus (SLE). Patients with HIV infection also have a high incidence of LA. Drugs such as procainamide, hydralazine, isoniazid, dilantin, phenothiazines, quinidine, and ACE inhibitors are known to induce LA.

Effects of Lupus Anticoagulant

- Some patients can be asymptomatic. Many elderly patients have lupus anticoagulant.
- LA is associated with antiphospholipid syndrome (APS or APLA). See APS for detailed clinical features.

Diagnosis

- Lupus anticoagulant should be suspected in cases of a markedly prolonged APTT without clinical bleeding. APTT fails to correct when the patient's plasma is mixed with normal plasma.
- The Russell viper venom (RVV) time is test of choice to detect the presence of lupus anticoagulant.
- Lupus anticoagulant can cause a false-positive VDRL test for syphilis.

Treatment

- Anticoagulant therapy should be started for patients with thrombosis. Heparin therapy is difficult to monitor due to already prolonged APTT and hence, low-molecular-weight heparin is preferred.

11 Nutritional Disorders

Q. Body mass index (BMI).

- Body mass index (BMI) is a measure of weight adjusted for height, calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Although BMI is often considered an indicator of body fatness, it is a surrogate measure of body fat because it measures excess weight rather than excess fat.

Uses of BMI

- BMI is a simple, inexpensive, and noninvasive surrogate measure of body fat which can be used bedside.
- BMI levels correlate with body fat and with future health risks. High BMI predicts future morbidity and death. Therefore, BMI is an appropriate measure for screening for obesity and its health risks.
- Use of BMI at the population level has resulted in an increased availability of published population data that allows public health professionals to make comparisons across time, regions, and population subgroups.

Limitations of BMI

- BMI is a surrogate measure of body fatness because it is a measure of excess weight rather than excess body fat.
- Factors such as age, sex, ethnicity, and muscle mass can influence the relationship between BMI and body fat.
- BMI does not distinguish between excess fat, muscle, or bone mass. For example, older adults tend to have more body fat than younger adults for an equivalent BMI. Women have more body fat than men with the same BMI. Muscular individuals may have a high BMI because of increased muscle mass.

Interpretation of BMI

BMI	Interpretation
Below 18.5	Underweight
18.5–24.9	Normal
25–29.9	Overweight
30–34.9	Mild obesity
35–39.9	Moderate obesity
>40	Extreme obesity

Alternatives to BMI

- Other measures of body fat, such as skinfold thicknesses, bioelectrical impedance, underwater weighing, and dual energy X-ray absorption, may be more accurate than BMI. But, most of these methods are cumbersome for routine clinical use.

Q. Discuss the assessment of nutritional status of a person.

- Nutrients are required for energy, growth, development, repair and maintenance of physiological/biochemical processes in the body. These nutrients are provided by the food that we eat. Of these, many are considered essential as they cannot be synthesized in the body and have to be supplied from outside.
- Undernutrition can lead to protein energy malnutrition, retarded growth, deficiencies of various vitamins and minerals. Elderly, pregnant or lactating women, and the poor and socially isolated are at particular risk for undernutrition.
- Overnutrition can lead to obesity with attendant increased risks of diabetes and cardiovascular diseases.

Nutritional Assessment

- Nutritional assessment is made by dietary history, anthropometric measurements, clinical examination, and laboratory tests.

Dietary History

- Economic status.
- Regularity and availability of meals.
- Recent changes in appetite, intake, or body weight.
- Use of special diets or dietary supplements.
- Use of alcohol, drugs, or medications.
- Food preferences and food allergies.
- Presence of illnesses affecting nutritional intakes, losses, or requirements.

- Quantification of dietary intake can be roughly made by twenty-four-hour diet recalls or a complete 3- to 5-day diet record.

Anthropometry

- This should include height, weight, body mass index, waist circumference and waist-hip ratio. Triceps skinfold thickness gives an idea about the amount of subcutaneous fat and mid arm muscle circumference about muscle bulk.
- BMI: Normal BMI is 18.5–24.9. BMI less than 18.5 is called undernutrition. BMI >30 is called obesity. BMI is less reliable in old age as height is lost.
- Patients with increased abdominal circumference (>102 cm in men and 88 cm in women) or with high waist-hip ratios (>1.0 in men and >0.85 in women) have a greater risk of diabetes mellitus, stroke, coronary artery disease, and early death.

Clinical Examination

- Look for muscle wasting, fat stores, volume status, and signs of nutrient deficiencies.

Laboratory Tests

- Serum albumin is low in protein-energy undernutrition.
- Fasting lipid profile (total cholesterol, HDL, triglycerides, LDL).
- Hemoglobin, blood glucose, and electrolytes.
- Many sophisticated techniques are available for assessment of muscle and fat composition of the body. These include bioelectrical impedance, dual-energy X-ray absorptiometry, air-displacement plethysmography, MRI and body line scanners.

Q. Discuss the classification, etiology, clinical features, investigations and management of malnutrition; protein energy malnutrition (PEM); undernutrition.

Q. Causes of weight loss.

- BMI less than <18.5 is called malnutrition or undernutrition.

Classification

BMI	Classification
17–18.5	Mild
16–17	Moderate
<16	Severe

Etiology of Undernutrition and Weight Loss

- Famine
- Endocrine disorders (hyperthyroidism, pheochromocytoma, adrenal insufficiency)
- Uncontrolled diabetes mellitus
- GI disorders (malabsorption syndromes, chronic pancreatitis, IBD, parasitic infestation)
- Malignancy
- Infections (tuberculosis, HIV, subacute bacterial endocarditis)
- COPD
- Chronic renal failure
- Psychiatric disorders (depression, mania, anorexia nervosa, schizophrenia)
- Chronic alcoholism
- Drugs (opiates, amphetamines, digoxin, metformin, NSAIDs, anticancer drugs)
- Treatment of obesity
- Anorexic drugs—amphetamines and derivatives
- Distance runners, models, ballet dancers, gymnasts
- Excessive physical activity (e.g. marathon runners)

Clinical Features

- In children, undernutrition (protein-energy malnutrition, PEM) is manifest as the syndromes of kwashiorkor (malnutrition with edema) and marasmus (malnutrition with marked muscle wasting).
- The clinical features of severe undernutrition in adults include:
  - Weakness, apathy, loss of initiative, depression, introversion.
  - Thirst, craving for food.
  - Weight loss.
  - Muscle wasting, loss of subcutaneous fat.
  - Amenorrhea or impotence.
  - Pale dry skin with loss of turgor.
  - Hair thinning or loss.
  - Cold and cyanosed extremities, pressure sores.
  - Edema, which may be present without hypoalbuminemia.
  - Subnormal body temperature, slow pulse, low blood pressure.
  - Distended abdomen, with diarrhea.
  - Diminished tendon jerks.
  - Susceptibility to infections (gastroenteritis, tuberculosis, skin infections, etc.).
  - In advanced starvation, patients become completely inactive and may assume a flexed, fetal position. In the last stage of starvation, death comes quietly and often quiet suddenly. All organs are atrophied at necropsy, except the brain.

Clinical features of specific nutrient deficiency

Nutrient	Features of deficiency
Vitamin A	Night blindness, xerophthalmia, ulceration and necrosis of the cornea (keratomalacia), perforation, endophthalmitis. Xerosis and hyperkeratinization of the skin
Vitamin D	Rickets, osteomalacia
Vitamin E	Areflexia, ataxia, ophthalmoplegia, hemolytic anemia.
Vitamin K	Coagulation disorder
Thiamin (vitamin B_1)	Beriberi, Wernicke-Korsakoff syndrome
Riboflavin (vitamin B_2)	Cheilosis, angular stomatitis, glossitis.
Niacin (vitamin B_3)	Pellagra (dementia, diarrhea, dermatitis)
Vitamin B_6 (pyridoxine)	Peripheral neuropathy, anemia
Biotin	Dermatitis, alopecia, paresthesiae
Vitamin B_{12} (Cobalamin)	Anemia, peripheral neuropathy, subacute combined degeneration.
Vitamin C (ascorbic acid)	Scurvy
Folate	Anemia
Iron	Anemia, platynychia, koilonychia
Iodine	Goiter
Calcium	Tetany, pathologic fractures due to osteomalacia, muscular irritability
Zinc	Anorexia, weakness, tingling, impaired taste

Investigations

- Mild anemia, leukopenia and thrombocytopenia. ESR is normal unless there is infection.
- Low blood glucose.
- Plasma free fatty acids are increased and there is ketosis and a mild metabolic acidosis.
- Albumin may be low but concentration is often normal because of normal liver function.
- Insulin secretion is low, glucagon and cortisol secretion is high.
- Urine has a fixed specific gravity and creatinine excretion becomes low.
- Tests of delayed skin hypersensitivity, e.g. to tuberculin, are falsely negative.
- ECG shows sinus bradycardia and low voltage.

Management

- People with mild malnutrition do not require any active treatment. Those with moderate malnutrition need extra feeding. Severe malnutrition needs hospital care.
- In severe malnutrition, initial efforts should be directed at correcting fluid and electrolyte abnormalities and infections. The second phase of treatment is directed at repletion of protein, carbohydrates, and micronutrients. In severe malnutrition, there is atrophy of the intestinal epithelium and of the exocrine pancreas, and the bile is dilute. Hence, refeeding should be initiated with small amounts of food which is easily digestible. Food should be palatable and similar to the usual staple meal, e.g. a cereal with some sugar, milk powder and oil. Either the enteral or parenteral route can be used, although the former is better.
- About 1500–2000 kcal/day will prevent progressive undernutrition, but additional calories are required to regain weight. A weight gain of 5% body weight per month is satisfactory. Patients should be followed up closely.

Q. Discuss the etiology, clinical features, complications, investigations and management of obesity.

- Obesity is defined as an excess of adipose tissue. Obesity is one of the most common disorders in medical practice and among the most frustrating and difficult to manage.
- Accurate quantification of body fat requires sophisticated techniques but physical examination is usually sufficient to detect excess body fat.
- BMI closely correlates with excess adipose tissue and obesity can be graded based on BMI.
- Abdominal obesity is a greater health hazard than generalized obesity. Visceral fat within the abdominal cavity is more hazardous to health than subcutaneous fat.

Etiology

Sedentary lifestyle	Enforced inactivity (postoperative) Aging
Dietary factors	Overeating High fat diets
Endocrine disorders	Hypothalamic disease Hypothyroidism Cushing's syndrome Polycystic ovary syndrome Hypogonadism Growth hormone deficiency Pseudohypoparathyroidism
Social factors	Low socioeconomic status
Psychiatric disorders	Night eating syndrome Binge eating
Genetic (dysmorphic) obesities	Autosomal recessive traits Autosomal dominant traits X-linked traits Chromosomal abnormalities
Drugs	Steroids Clozapine Amitriptyline Cyproheptadine Thiazolidinediones Grading of obesity

Grading of Obesity

BMI	Classification
18.5–24.9	Normal
25–29.9	Overweight
30–34.9	Mild obesity
35–39.9	Moderate obesity
>40	Extreme obesity

Complications of Obesity

- Hypertension.
- Type 2 diabetes mellitus.
- Hyperlipidemia.
- Coronary artery disease.
- Degenerative joint disease (osteoarthritis).
- Increased incidence of cancers (colon, rectum, and prostate in men; uterus, biliary tract, breast, and ovary in women).
- Thromboembolic disorders.
- Digestive tract diseases (gallstones, reflux esophagitis).
- Non-alcoholic steatohepatitis (NASH).
- Obstructive sleep apnea.
- Respiratory failure (pickwickian syndrome).
- Psychosocial problems (low self-esteem, depression).
- Varicose veins.

Clinical Assessment

History

- Age of onset, recent weight changes, family history of obesity, occupational history, eating and exercise behavior, cigarette and alcohol use.
- History of any depression and eating disorders.
- Use of any drugs and nutritional supplements.

Physical Examination

- Degree and distribution of body fat, overall nutritional status, and signs of secondary causes of obesity.
- Look for any complication of obesity such as hypertension, atherosclerosis, etc.

Investigations

- Blood sugar
- Lipid profile (low-density lipoprotein (LDL) and HDL cholesterol, and triglycerides should be measured).
- Urea, creatinine.
- Electrolytes.
- Thyroid function tests and other endocrine work up if necessary.
- ECG to look for evidence of coronary artery disease.

Treatment

- Treatments for obesity either decrease energy intake or increase energy expenditure.

Dietary Therapy

- Low-fat, high-complex carbohydrate, high-fiber diet.
- Avoid foods with high calories without other nutrients, i.e. fat, sucrose, and alcohol.

Exercise

- Increasing energy expenditure through physical activity helps in losing weight. Aerobic exercise is particularly useful for long-term weight maintenance. When compared with no treatment, exercise alone results in small amounts of weight loss. Exercise plus diet results in greater weight loss than diet alone. A greater intensity of exercise causes greater amount of weight loss. Up to 1 hour of moderate exercise per day is associated with long-term weight maintenance in individuals who have successfully lost weight.

Drug Therapy

- Drug therapy may be considered for those with a BMI greater than 30 or those with BMI >27 with comorbid conditions. Obesity drugs may be used as part of a comprehensive weight loss program.
- Medications for obesity include two major categories: Appetite suppressants (anorexiants) and gastrointestinal fat blockers. Appetite-suppressing medications include phentermine, diethylpropion, and mazindol. Two new appetite suppressants have been approved; lorcaserin and phentermine/topiramate. Lorcaserin is a selective 5-HT2C receptor agonist. Phentermine reduces the appetite by satiety-center stimulation in hypothalamic and limbic areas of the brain.
- Gastrointestinal fat blockers (e.g. orlistat) reduce the absorption of fat from the gastrointestinal tract. Orlistat reduces fat absorption in the gastrointestinal tract. It can cause diarrhea, oily stools, and reduced absorption of fat-soluble vitamins. The recommended dose of orlistat is 120 mg three times daily with meals.

Liposuction

- Removal of fat by aspiration after injection of saline has been used to remove and contour subcutaneous fat. However, it does not improve insulin sensitivity or risk factors for coronary heart disease.

Surgery

- Bariatric surgery is a treatment option for patients with severe obesity (BMIs over 40, or over 35 if obesity-related comorbidities are present). These are as follows:

- *Gastric banding*—this is a purely restrictive procedure that compartmentalizes the upper stomach by placing a tight, adjustable prosthetic band around the entrance to the stomach. Gastric banding results in less dramatic weight loss than Roux-en-Y gastric bypass (RYGB) and fewer short-term complications. Frequent follow-up is required to adjust the gastric band.

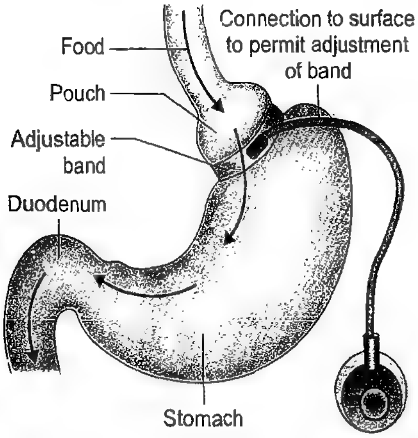


Fig. 11.1: Gastric banding

- *Roux-en-Y gastric bypass (RYGB)*—here a small proximal gastric pouch is created and connected to the rest of the gastrointestinal tract via a tight stoma and a Roux-en-Y small bowel arrangement. RYGB results in substantial amounts of weight loss. Complications include peritonitis due to anastomotic leak, abdominal wall hernias, staple line disruption, gallstones, neuropathy, marginal ulcers, stomal stenosis, wound infections, thromboembolic disease, gastrointestinal symptoms, and nutritional deficiencies.

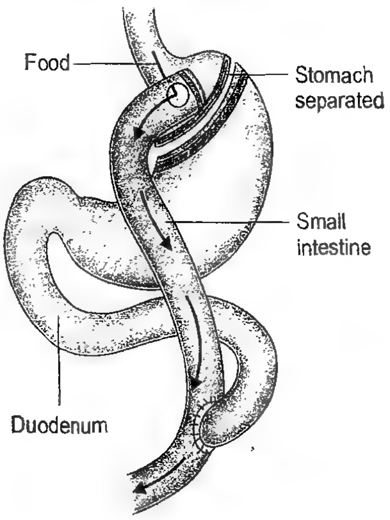


Fig. 11.2: Roux-en-Y gastric bypass

- *Vertical banded gastroplasty*—this is a restrictive procedure in which the upper part of the stomach is partitioned by a vertical staple line with a tight outlet wrapped by a prosthetic mesh or band. It is often referred to as a stomach stapling operation. The small proximal pouch gets filled quickly by food and prevents consumption of a large meal.

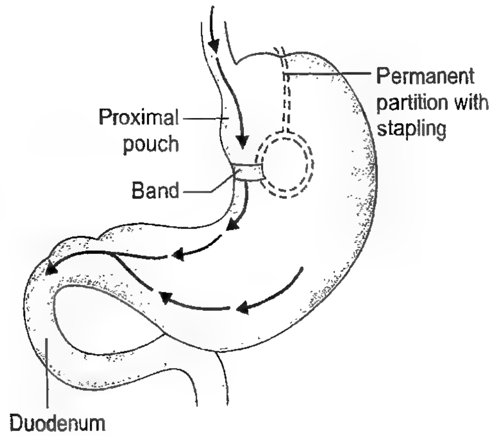


Fig. 11.3: Vertical banded gastroplasty

Q. Vitamin A (retinol) deficiency.

- Vitamin A is lipid soluble and is found in three forms: Retinols, beta-carotenes, and carotenoids. Retinol, also known as preformed vitamin A, is the most active form and is mostly found in animal sources of food. Beta-carotene, also known as provitamin A, is the plant source of retinol.
- Vitamin A was the first fat-soluble vitamin to be discovered.
- The recommended daily intake of vitamin A is 800 to 1000 μg.

Functions of Vitamin A

- Night vision.
- Differentiation of epithelial cells.
- Normal growth, fetal development, fertility, hematopoiesis and immune function.

Causes of Vitamin A Deficiency

- *Prolonged dietary deprivation*: It is endemic in areas such as Southern and Eastern Asia, where rice, devoid of β-carotene, is the staple food.
- *Decreased bioavailability* of provitamin A carotenoids.
- *Interference with absorption or storage*: Celiac disease, cystic fibrosis, pancreatic insufficiency, duodenal bypass, chronic diarrhea, bile duct obstruction, giardiasis, and cirrhosis.

Clinical Features of Vitamin A Deficiency

- Vitamin A deficiency is an important cause of blindness globally especially in Asia.
- Night blindness is the earliest sign due to an impairment of the dark adaptation process.

- Xerophthalmia is caused by inadequate function of the lacrimal glands and is characterized by Bitot's spots, corneal xerosis and keratomalacia.
- Bitot's spots—these are glistening white plaques of desquamated thickened conjunctival epithelium, usually triangular in shape and firmly adherent to the conjunctiva.
- Keratomalacia is the final consequence of deficiency and leads to corneal ulceration, scarring and irreversible blindness.
- Poor bone growth.
- Dermatological abnormalities, such as hyperkeratosis and phrynoderma (follicular hyperkeratosis).
- Impairment of humoral and cell-mediated immunity via direct and indirect effects on the phagocytes and T cells.

Investigations

- Serum retinol level is low. A value of less than 0.7 mg/L in children younger than 12 years is considered low.
- A serum RBP (retinol binding protein) is less expensive than a serum retinol study. Level is low in vitamin A deficiency.

Treatment

- For treatment of xerophthalmia, vitamin A is given in three doses. The first dose (2 lakh U) is given immediately on diagnosis, the second on the following day, and the third dose at least two weeks later. If there is vomiting or severe diarrhea, vitamin A is given by intramuscular injection.
- In countries where vitamin A deficiency is endemic, pregnant women should be advised to eat dark green leafy vegetables and yellow fruits. A single prophylactic oral dose (2 lakh U) is given to pre-school children. Repeated oral administration of these doses to children every 4–6 months is used in some endemic areas.

Q. Hypervitaminosis A; vitamin A toxicity.

- Acute toxicity occurs in adults if >6 lakh units of vitamin A is ingested. Symptoms include nausea, vomiting, increased intracranial pressure, skin desquamation, vertigo, and blurry vision (pseudotumor cerebri). In very high doses, drowsiness, malaise, and recurrent vomiting can follow the above symptoms. In infants under six months of age, even 20,000 IU may produce toxic effects.
- The most serious side-effects of repeated moderate or high doses of retinol are liver damage, hyperostosis and teratogenicity. Women in developed countries who are pregnant are therefore advised not to take vitamin A supplements.
- Excessive intake of carotene can cause skin discoloration (hypercarotenosis). It gradually fades when the excessive intake is stopped.

Q. Beriberi.

Q. Vitamin B_1 (thiamine) deficiency.

Q. Wernicke-Korsakoff syndrome.

- Thiamine is found in larger quantities in yeast, legumes, pork, rice, and cereals.

Activity

- Thiamine is required for carbohydrate metabolism. Thiamine pyrophosphate (TPP) is an essential co-enzyme in the conversion of pyruvate to acetyl CoA. This is the bridge between glycolysis and the tricarboxylic acid (Krebs) cycle.
- TPP is also the co-enzyme for transketolase of the pentose phosphate pathway.
- Thiamine is also important for nerve impulse conduction.

Thiamine Deficiency

- Cells cannot metabolize glucose aerobically leading to accumulation of pyruvic and lactic acids, which produce vasodilatation and increased cardiac output. There is also less ATP generation.
- Thiamine deficiency is mainly seen in chronic alcoholics due to poor diet and impaired absorption. Deficiency is also seen in people eating mainly polished rice.

Clinical Features

- *Infantile beriberi* is seen in exclusively breastfed infants of thiamine-deficient mothers, and is invariably fatal.
- *Dry beriberi* mainly affects nervous system and is characterized by peripheral neuropathy with wrist and/or foot drop, Wernicke's disease and Korsakoff's psychosis. Wernicke's disease is a triad of nystagmus, ophthalmoplegia, and ataxia, along with confusion. Korsakoff's psychosis is impaired short-term memory and confabulation with otherwise grossly normal cognition. These two are almost exclusively seen in alcoholics with thiamine deficiency.
- *Wet beriberi* mainly affects heart and causes congestive cardiac failure with pulmonary and peripheral edema.

Treatment

- Thiamine is given at a dose of 50 to 100 mg for 7 to 14 days IV or IM. Then an oral dose of 10 mg per day is given until full recovery is achieved.
- Korsakoff's psychosis is irreversible and does not respond to thiamine treatment.

Q. Niacin deficiency (pellagra).

- Niacin is a generic term for nicotinic acid and other derivatives with similar nutritional activity. Niacin is an essential component of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are involved in many oxidation-reduction reactions.
- The major food sources of niacin are protein foods, cereals, vegetables, and dairy products. It is also synthesized by the body in small amounts from tryptophan.

Causes of Niacin Deficiency

- Pellagra is now uncommon except in parts of Africa, alcoholics and in patients with anorexia nervosa, or malabsorptive disease.
- Pellagra can occur in Hartnup's disease which is characterized by impaired absorption of several amino acids, including tryptophan.
- It may also be seen in carcinoid syndrome, where tryptophan is utilized for the production of 5-HT rather than the synthesis of niacin.

Deficiency (Pellagra)

- Pellagra (meaning "raw skin") is characterized by three Ds: Dermatitis, diarrhea, and dementia.
- *Dermatitis* appears as erythema resembling severe sunburn, symmetrically over the parts of the body exposed to sunlight, particularly the dorsum of hands and feet, and neck are involved (Casal's necklace). Skin lesions are dark, dry, and scaling.
- *Diarrhea* is often associated with glossitis, stomatitis and dysphagia, reflecting the presence of inflammation throughout the gastrointestinal tract.
- *Dementia* begins with lethargy, insomnia and irritability, and progresses to confusion, memory loss, hallucinations, and psychosis.

Treatment

- Nicotinamide is given in a dose of 100 mg 8-hourly by mouth or by the parenteral route for 5 days.
- Intake of diet rich in niacin such as meats, milk, peanuts, green leafy vegetables, whole or enriched grains, and brewers' dry yeast.

Q. Vitamin B_{12} deficiency

- Vitamin B_{12} deficiency causes megaloblastic anemia, and neurological degeneration.
- Vitamin B_{12} is required for the integrity of myelin. In severe deficiency there is demyelination. It may be clinically manifest as peripheral neuropathy or spinal cord degeneration affecting both posterior and lateral columns (subacute combined degeneration of the spinal cord). In addition, there may be cerebral manifestations (resembling dementia) or optic atrophy.
- Treatment is with parenteral hydroxocobalamin.
- Vitamin B_{12} is discussed in detail in hematology chapter.

Q. Vitamin C (ascorbic acid) deficiency; scurvy.

- Vitamin C plays a role in collagen, carnitine, hormone, and amino acid formation. It is essential for wound healing and facilitates recovery from burns. Vitamin C is also an antioxidant, supports immune function, and facilitates the absorption of iron.
- It takes part in the hydroxylation of proline and lysine to hydroxyproline and hydroxylysine which is present in collagen.
- Ascorbic acid is present in fresh fruit and vegetables. It is very easily destroyed by heat. Hence, many traditional cooking methods reduce or eliminate it.

Causes of Deficiency

- Lack of dietary fruit and vegetables >2 months
- Infants fed exclusively on boiled milk
- Severely malnourished individuals
- Drug and alcohol abusers
- Extreme poverty
- Smoking

- Defective formation of collagen impairs wound healing, causes capillary hemorrhage and reduced platelet adhesiveness (normal platelets are rich in ascorbate).

Clinical Features

- Severe deficiency causes scurvy.
- Symptoms develop after weeks to months of vitamin C depletion. Lassitude, weakness, irritability, weight loss, and vague myalgias and arthralgias may develop early.
- Gums become swollen, purple, spongy, friable and bleed easily. Eventually, teeth become loose and avulsed.
- Other features are perifollicular hemorrhages, petechiae and purpura, splinter hemorrhages, hemarthroses, and subperiosteal hemorrhages. Intracerebral hemorrhage can cause death.
- Anemia.
- Impaired wound healing.

Diagnosis

- It is based on clinical features. Serum ascorbic acid levels of <0.2 mg/dl (<11 μmol/L) indicate vitamin C deficiency, but this test is not routinely done.

Treatment

- Scurvy is treated with 300–1000 mg of ascorbic acid orally per day.
- Eating raw fruits and vegetables especially citrus fruits.

Q. Fluorosis.

- Excess fluoride consumption (water fluoride content >3 to 5 ppm) can cause fluorosis or hypomineralization of the dental enamel. The mechanism by which excessive fluoride causes fluorosis is not fully understood.
- The earliest signs of fluorosis are chalky-white patches on the surface of the enamel. These patches become stained yellow or brown, producing a characteristic mottled appearance. Severe toxicity weakens the enamel, pitting its surface and teeth become brittle and easily breakable.
- Other features are sclerosis of the bones, especially of spine, pelvis and limbs. Ligament and tendon calcification also can occur.
- Fluorosis is primarily a cosmetic concern, but it can make the teeth more susceptible to wear and breakage. Fluorosis can be prevented by avoiding excess fluoride consumption (e.g. avoiding swallowing of fluoridated toothpaste or mouth rinses).

Q. Vitamin D deficiency.

- Vitamin D is a fat-soluble vitamin. There are two chemical forms of vitamin D; ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Ergocalciferol (vitamin D_2) is present in food. Cholecalciferol (vitamin D_3) is synthesized in the skin on exposure to sunlight from 7-dehydrocholesterol.
- Natural dietary sources of vitamin D include egg yolk, liver, fatty fish, butter and milk.
- Vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D (calcidiol), which is the major circulating form of vitamin D and is the best index of vitamin D levels. Calcidiol is hydroxylated in the kidney to 1, 25-dihydroxyvitamin D (calcitriol), which is the most active form.
- Vitamin D deficiency is present when serum levels of 25-hydroxyvitamin D is less than 20 ng/ml.
- Vitamin D deficiency produces defective mineralization of bone, leading to rickets in children and osteomalacia in adults.
- A minimum intake of 200 IU of vitamin D per day is recommended for adults. For pregnant and lactating women, a minimum of 400 IU per day is recommended.

Actions

- Vitamin D has a variety of actions on calcium, phosphate, and bone metabolism.
- It increases serum calcium and phosphate concentration by increasing intestinal calcium and phosphate absorption, increasing renal calcium reabsorption, and enhancing PTH-mediated bone resorption.,

Causes of Vitamin D Deficiency

Deficient intake
- Dietary
- Inadequate sunlight exposure

Decreased absorption
- Gastrectomy
- Small bowel disease
- Pancreatic insufficiency

Loss of vitamin D binding protein
- Nephrotic syndrome

Defective 25-hydroxylation
- Cirrhosis of liver

Defective 1-alpha 25-hydroxylation
- Hypoparathyroidism
- Renal failure
- 1-alpha hydroxylase deficiency

Defective target organ response to calcitriol
- Hereditary vitamin D-resistant rickets

Clinical Features of Vitamin D Deficiency

- Vitamin D deficiency causes rickets in children and osteomalacia in adults. For details, see the following pages.

Investigations

- 25-hydroxyvitamin D level will be low. A level of less than 20 ng/ml indicates vitamin D deficiency.
- Serum parathyroid hormone level will be elevated. But PTH measurement is not routinely required.

Treatment of Vitamin D Deficiency

- Initial treatment with 50,000 units of vitamin D_2 or D_3 orally once per week for six to eight weeks, and then 800 to 1000 IU of vitamin D_3 daily thereafter. Vitamin D_3 is better than vitamin D_2 for vitamin D supplementation. Loading dose is not recommended in pregnant women.
- All patients should maintain a daily calcium intake of at least 1000 mg per day.

Q. Osteomalacia.

- Osteomalacia is characterized by defective bone mineralization, bone pain, myopathy, increased bone fragility and fractures.

- Osteomalacia has to be differentiated from osteoporosis. Osteoporosis refers to decreased bone mass due to imbalance between bone formation and bone resorption. In osteoporosis, the bones are porous and brittle, whereas in osteomalacia the bones are soft. Osteopenia is a condition in which bone mineral density is lower than normal, but not severe enough to call it as osteoporosis. Osteopenia is a precursor to osteoporosis.

Etiology

Vitamin D deficiency
- Deficient intake
- Malabsorption
- Inadequate sunlight exposure
- Loss of vitamin D binding protein (nephrotic syndrome)
- Defective 25-hydroxylation (e.g. cirrhosis of liver)
- Defective 1-alpha 25-hydroxylation (e.g. renal failure)
- Vitamin D-resistance

Mineralization defects
- Abnormal matrix
- Chronic renal failure
- Inhibitors of mineralization (fluoride, aluminum, bisphosphonates)

Phosphate deficiency
- Decreased intake
- Antacids
- Impaired renal reabsorption (e.g. Fanconi syndrome)

Clinical Features

- It can be asymptomatic and present radiologically as osteopenia.
- It can also produce diffuse bone pain and tenderness and muscle weakness.
- Muscle weakness is characteristically proximal and may be associated with muscle wasting, hypotonia, and discomfort with movement.
- Fractures may occur with a little or no trauma.
- Bone deformities can occur in severe osteomalacia of long duration.

Investigations

- *Radiologic findings*
  - Reduced bone density with thinning of the cortex.
  - Changes in vertebral bodies—loss of radiologic distinctness of the vertebral body trabeculae, concavity of the vertebral bodies, the codfish vertebrae. The vertebral disks appear large and biconvex. There may be spinal compression fractures.
  - Looser zones—these are pseudofractures, fissures, or narrow radiolucent lines, two to five mm in width with sclerotic borders, and are the characteristic radiologic finding in osteomalacia. They often are bilateral and symmetric and lie perpendicular to the cortical margins of bones. They are usually found at the femoral neck, femoral shaft, and the pubic and ischial rami. They may also occur at the ulna, scapula, clavicle, rib and metatarsal bones. The term "Milkman syndrome" refers to the combination of multiple, bilateral and symmetric pseudofractures in a patient with osteomalacia.
- Patients with vitamin D deficiency have low levels of 25-hydroxyvitamin D, hypophosphatemia, and low calcium concentration.
- Serum phosphorus level may also be low in hypophosphatemic rickets.
- ALP is low in hypophosphatemic osteomalacia and normal or high in hypocalcemic osteomalacia.

Treatment

- Underlying cause should be treated.
- Correction of hypophosphatemia, hypocalcemia, and vitamin D deficiency.

Q. Rickets.

- Rickets refers to the changes caused by deficient mineralization at the growth plate. It occurs in children. Osteomalacia refers to impaired mineralization of the bone matrix and occurs in adults.
- Hypocalcemic rickets is due to calcium deficiency.
- Hypophosphatemic rickets is due to phosphate deficiency.

Etiology

- Same as osteomalacia.

Clinical Manifestations

- Rickets manifests initially at sites of rapid bone growth such as distal forearm, knee, and costochondral junctions.

Skeletal Findings

- Delay in the closure of the fontanelles.
- Parietal and frontal bossing.
- Craniotabes (soft skull bones).
- Enlargement of the costochondral junction visible as beading along the anterolateral aspects of the chest (the "rachitic rosary").
- Development of Harrison sulcus caused by the muscular pull of the diaphragmatic attachments to the lower ribs.
- Enlargement of the wrist and bowing of the distal radius and ulna.
- Progressive lateral bowing of the femur and tibia.

Extraskeletal Findings

- Decreased muscle tone, seizures, increased sweating and hypoplasia of the dental enamel are seen in hypocalcemic rickets.
- Abscesses of the teeth occur in hypophosphatemic rickets.

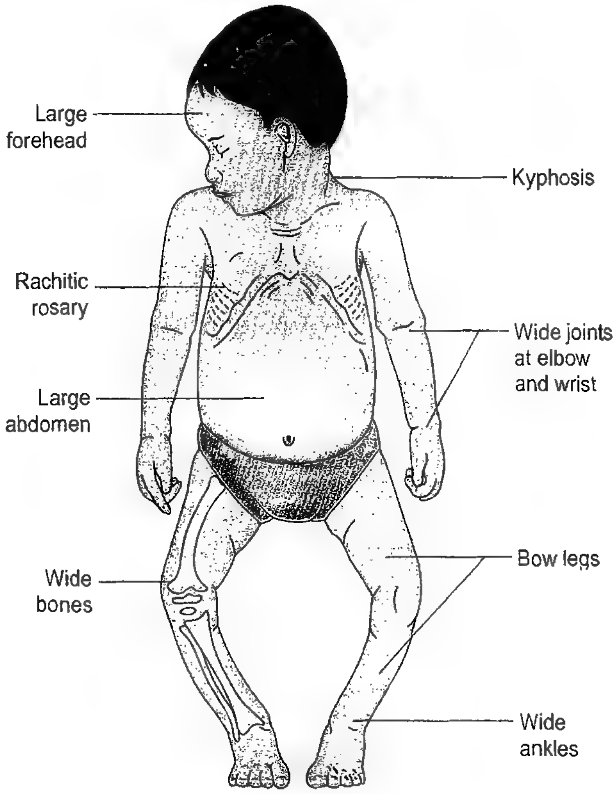


Fig. 11.4: Clinical features of rickets

Laboratory Findings

- Alkaline phosphatase is markedly increased.
- Serum phosphorus concentration is usually low in both hypocalcemic and hypophosphatemic rickets.
- Serum calcium concentration is low in hypocalcemic rickets.
- Parathyroid hormone level is elevated in hypocalcemic rickets and normal in hypophosphatemic rickets.
- Serum concentration of 25-hydroxyvitamin D is low in vitamin D deficiency.
- Measurement of serum creatinine to exclude renal insufficiency as the primary etiology.
- Measurement of liver enzymes to exclude liver disease as the etiology of elevated alkaline phosphatase activity.
- *Radiographic findings*
  - Widening of the epiphyseal plate and loss of definition of the zone of provisional calcification at the epiphyseal/metaphyseal interface.
  - Disorganization of the growth plate with cupping, splaying, formation of cortical spurs, and stippling.
  - Delayed appearance of epiphyseal bone centers.
  - The shafts of the long bones are osteopenic, with thin cortex. Trabecular pattern is reduced and becomes coarse. Bone deformities are usually present and in severe rickets, pathological fractures and looser zones may be noted.

Treatment

- Rickets caused by vitamin D deficiency is treated with vitamin D_2 or vitamin D_3 and calcium supplementation daily. After 3–4 months, the dose of vitamin D is reduced to a maintenance level.
- Treatment of hypophosphatemic rickets is with phosphate supplements, combined with vitamin D to promote intestinal calcium and phosphate absorption.

Q. Discuss the etiology, clinical features, investigations and management of osteoporosis.

- Osteoporosis is characterized by a decrease in the amount of bone. The rate of bone formation is often normal, whereas the rate of bone resorption is increased.
- Osteoporosis is associated with increased risk of fractures especially the spine and hip. It is a leading cause of morbidity and mortality in elderly people.

Etiology

Endocrine disorders
- Hyperparathyroidism
- Cushing's syndrome
- Hypogonadism
- Thyrotoxicosis
- Vitamin D deficiency
- Estrogen deficiency (postmenopausal)
- Growth hormone deficiency
- Diabetes mellitus

Gastrointestinal diseases
- Gastrectomy
- Malabsorption syndromes
- Inflammatory bowel disease
- Chronic biliary tract obstruction

Malignancies
- Multiple myeloma
- Lymphoma
- Leukemia
- Disseminated carcinoma

Genetic disorders
- Osteogenesis imperfecta
- Ehlers-Danlos syndrome
- Marfan's syndrome
- Homocystinuria

(contd.)

Drugs
- Alcohol
- Tobacco
- Steroids
- Heparin
- Phenytoin
- Chemotherapy

Miscellaneous causes
- Anorexia nervosa
- Hypercalciuria
- Immobilization
- Rheumatoid arthritis
- Pregnancy and lactation
- Senile osteoporosis

Clinical Features

- Usually asymptomatic unless there is fracture.
- Backache or spontaneous fracture or collapse of vertebra.

Investigations

- X-rays show osteopenia.
- Serum calcium and phosphate to rule out hypocalcemia.
- ALP may be slightly elevated, following a fracture.
- Parathyroid hormone level to screen for primary hyperparathyroidism.
- Serum 25-hydroxyvitamin D levels.
- Thyroid function tests.
- Serum testosterone in men (hypogonadism).
- Tissue transglutaminase antibodies to screen for celiac disease.
- Serum and urine protein electrophoresis to rule out multiple myeloma.
- 24-hour urinary free cortisol if features of Cushing's syndrome are present.
- Bone densitometry using dual energy X-ray absorptiometry (DEXA).

Treatment

General Measures

- Good diet containing adequate protein, calories, calcium, and vitamin D.
- Physical activity increases bone density.
- Subjects who already have osteoporosis should take precautions to avoid falls (e.g. adequate lighting, handrails on stairs, handholds in bathrooms).
- Bedridden patients should be given active or passive exercises.
- Alcohol and smoking should be avoided.
- If on steroids, dose should be reduced or discontinued if possible.

Specific Measures

- Treatment is indicated for all patients with osteoporosis and for those who have had fragility fractures. Prophylactic treatment should also be considered for patients with advanced osteopenia.
- *Vitamin D and calcium supplementation*—oral vitamin D is given in doses of 800–1000 IU daily and calcium supplementation in a dose of 1200 to 1500 mg/day including dietary consumption.
- *Bisphosphonates*—they inhibit osteoclast-induced bone resorption and reduce the incidence of both vertebral and nonvertebral fractures. Both oral and parenteral bisphosphonates are available. Examples are alendronate, risedronate, zoledronic acid and pamidronate. Osteonecrosis of the jaw has been associated with use of bisphosphonates; however, this condition is rare in patients taking oral bisphosphonates.
- *Hormone replacement therapy*—low doses of estrogen in postmenopausal women can prevent osteoporosis without causing much adverse effects. Men with hypogonadism may be treated with testosterone.
- Selective estrogen receptor modulators—raloxifene, 60 mg/d orally, can be used by postmenopausal women instead of estrogen for the prevention of osteoporosis. Unlike estrogen, raloxifene does not cause endometrial hyperplasia, uterine bleeding, or cancer. The risk of breast cancer is also reduced. However, since raloxifene is a potential teratogen, it is contraindicated in premenopausal women. It also increases the risk of thromboembolism.
- *Calcitonin*—a nasal spray of calcitonin is available. The usual dose is one puff once daily. It decreases bone resorption.
- *Teriparatide*—this is an analog of PTH. It stimulates production of new bone matrix that must be mineralized. Patients should take sufficient vitamin D and calcium along with this drug. When given to patients with osteoporosis daily subcutaneously for 2 years, teriparatide dramatically improves bone density. Hypercalcemia is a risk with this medicine. Following a course of teripatitide, a course of bisphosphonates should be considered to retain the improved bone density.

Q. Hypervitaminosis D.

- Vitamin D intoxication may occur in fad dieters who consume "megadoses" of supplements or in patients on vitamin D replacement therapy. Empirical administration of very high doses of intramuscular vitamin D injections at frequent intervals is one of the most common causes of hypervitaminosis D. Other causes are primary hyperparathyroidism, MEN I and II syndrome, malignancies

such as Hodgkin's lymphoma and non-Hodgkin's lymphoma, granulomatous diseases like sarcoidosis and tuberculosis.

- The upper limit of vitamin D intake is 2000 IU daily.

Clinical Features

- Vitamin D excess can result in hypercalcemia, hypercalciuria, confusion, polyuria, polydipsia, anorexia, vomiting, muscle weakness, and bone demineralization with pain.
- Widespread metastatic calcifications can occur in the kidney, lung, gastric mucosa and blood vessels. Hypertension and renal failure may result.

Investigations

- Serum 25-hydroxyvitamin D level is >100 ng/ml. Serum calcium and urine calcium levels are high.

Treatment

- Restriction of dietary calcium intake and appropriate attention to hydration.
- Discontinuation of vitamin D, usually leads to resolution of hypercalcemia.
- Prednisone may help reduce plasma calcium levels by reducing intestinal calcium absorption.
- Bisphosphonate therapy can be usefully added to the regime.

12 Psychiatric Disorders

Q. Give the classification of psychiatric disorders.

- Psychiatric disorders are central nervous system diseases characterized by disturbances in emotion, cognition, motivation, and socialization.
- All psychiatric disorders currently lack well-defined neuropathology and bona fide biologic markers. Therefore, diagnoses continue to be made solely from clinical features.
- The following classification of psychiatric disorders is from 'The Diagnostic and Statistical Manual of Mental Disorders', Fifth Edition (DSM-5).
  - Neurodevelopmental disorders
  - Schizophrenia and other psychotic disorders
  - Bipolar and related disorders
  - Depressive disorders
  - Anxiety disorders
  - Obsessive-compulsive and related disorders
  - Trauma- and stressor-related disorders
  - Dissociative disorders
  - Somatic symptom and related disorders
  - Feeding and eating disorders
  - Elimination disorders
  - Sleep-wake disorders
  - Sexual dysfunctions
  - Gender dysphoria
  - Disruptive, impulse-control, and conduct disorders
  - Substance-related and addictive disorders
  - Neurocognitive disorders
  - Personality disorders
  - Paraphilic disorders
  - Other mental disorders

Q. Psychosis.

Q. Brief psychotic disorder.

- Psychotic disorders are characterized by delusions, hallucinations, disorganized thinking, motor behavior abnormalities (including catatonia), and negative symptoms.
- It includes schizophrenia and other psychotic disorders.
- Brief psychotic disorder consists of delusions, hallucinations, or other psychotic symptoms for at least 1 day but <1 month. It is typically caused by severe stress in susceptible people. If psychotic symptoms last more than 1 month, then it is called schizophrenia.

Clinical Features

- *Hallucinations*—these are false sensory perceptions occurring in any of the five sensory modalities. Auditory hallucinations are the most common, followed by visual, tactile, olfactory, and gustatory.
- *Delusions*—false beliefs that are firmly held despite obvious evidence to the contrary, and not typical of the patient's culture, faith, or family, are classified as delusions. Examples are persecutory, grandiose, religious, somatic, and other delusions.
- *Thought disorganization*—disruption of the logical process of thought may manifest as nonsensical speech, or bizarre behavior. Disorganized thinking may prevent the patient from giving a coherent history or meaningful consent to treatment.
- *Agitation*—agitation is an acute state of anxiety, heightened emotional arousal, and increased motor activity.
- *Aggression*—acts or threats of violence may occur in patients with persecutory delusions, thought disorganization, and poor impulse control.

Disorders associated with psychotic features

- Schizophrenia.
- Bipolar mania.
- Major depression with psychotic features.
- Alzheimer's disease.
- Delirium.
- Substance induced psychotic disorder (e.g. alcohol. illicit drugs, withdrawal of alcohol or sedative/hypnotic drugs).

- Psychosis secondary to a medical condition (CNS infections, seizures, endocrine problems, hypoxia, hypercarbia, hypoglycemia, fluid or electrolyte abnormalities, hepatic and renal disorders).

Treatment

- Antipsychotic drugs are the mainstay of treatment. Examples of antipsychotic drugs are risperidone, olanzapine, quetiapine, clozapine, etc.
- Psychological treatment.

Q. Discuss the etiology, clinical features and management of schizophrenia.

Q. Enumerate the positive symptoms (first rank symptoms) of schizophrenia.

- Schizophrenia is a psychotic disorder characterized by hallucinations (false perceptions), delusions (false beliefs), disorganized speech and behavior, flattened affect (restricted range of emotions), cognitive deficits (impaired reasoning and problem solving), and occupational and social dysfunction.
- It is one of the most disabling and economically catastrophic disorder, because of lifelong course, debilitating symptoms, and lack of social acceptability.
- The term schizophreniform disorder describes patients who meet the symptom requirements but not the duration requirements for schizophrenia, and schizoaffective disorder is used for those who manifest symptoms of schizophrenia and independent periods of mood disturbance.

Etiology

- *Genetic factors*—schizophrenia can be transmitted genetically. There is 50% concordance rate between monozygotic twins and 10% concurrence rate for first-degree relatives.
- *Environmental factors*—advanced paternal age, first and second trimester insults to fetal development, including viral infection, starvation, and toxic exposure, perinatal insults such as anoxia and birth trauma are associated with an increased risk of schizophrenia.
- Exposure to psychoactive drugs in adolescence and young adulthood.
- *Psychological stresses*—adverse life events and highly emotional family environment may precipitate episodes of schizophrenia.
- Hyperactivity of dopaminergic projections from the midbrain to the anterior cortex, decrease in prefrontal activity of dopaminergic pathways and alterations in glutamate and GABA neurotransmission in the prefrontal cortex has been noted in schizophrenic patients.
- Structural abnormalities of the brain—schizophrenic brains are smaller than normal brains, with enlarged ventricles.
- Schizophrenia can be associated with temporal lobe epilepsy, Huntington's chorea, cerebral tumors and demyelinating diseases. This is known as symptomatic schizophrenia.

Clinical Features

Positive Symptoms (First Rank Symptoms)

- Positive symptoms are synonymous with psychosis. "Positive" refers to the active quality of these symptoms and are of the 'first rank' in importance when making the diagnosis of schizophrenia. These can be remembered by the mnemonic ABCD.
  - *A: Auditory hallucinations*: These are commonly of voices heard outside the head that talk to or about the person. Sometimes the voices repeat the person's thoughts. Hallucinations of other sensory modalities also occur.
  - *B: Broadcasting, insertion/withdrawal of thoughts*: Disturbances of the normal private boundary of thinking manifests as belief that their thoughts are being broadcast to others and others thoughts are being 'inserted' into their mind.
  - *C: Control of feelings, impulses or acts by others.*
  - *D: Delusions.*

Negative Symptoms

- *Flattened (blunted) affect*—this is loss of capacity to express feelings, resulting in a blank appearance, monotonous voice, and absence of meaningful gestures.
- *Apathy and loss of drive (avolition)*—to involve in constructive activity, social interaction, and recreation, etc.
- *Social inattention*—includes a loss of interest in interactions with family, friends, colleagues, neighbors, and others.
- *Poverty of speech*—decreased speech and terse replies to questions, creating the impression of inner emptiness. The speech may be circumstantial (i.e. the patient takes a long time and uses many words in answering a question) or tangential (i.e. the patient speaks at length but never actually answers the question).
- *Poor self-care.*

Other Symptoms

- *Catatonia*—this refers to adoption of awkward postures for prolonged periods.

Diagnostic Criteria

- *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5)* criteria for the diagnosis of schizophrenia are as follows:
  - Patient must have experienced at least two of the following symptoms:
    - Delusions
    - Hallucinations
    - Disorganized speech
    - Disorganized or catatonic behavior
    - Negative symptoms
  - At least 1 of the symptoms must be the presence of delusions, hallucinations, or disorganized speech.
  - Continuous signs of the disturbance must persist for at least 6 months, during which the patient must experience at least 1 month of active symptoms (or less if successfully treated), with social or occupational deterioration problems occurring over a significant amount of time. These problems must not be attributable to another condition.

Management

Antipsychotic Agents

- Antipsychotics (also called neuroleptics) may be divided into conventional (typical, or first-generation) drugs such as chlorpromazine and haloperidol, and newer (atypical, or second-generation) drugs such as clozapine, olanzapine, quetiapine and risperidone.
- These drugs work by blocking D_2 dopamine receptors in the brain. Newer drugs also block 5-HT2 receptors and are less likely to produce extrapyramidal side-effects, but clozapine can cause agranulocytosis and requires regular monitoring of WBC count.
- They take 2–3 weeks to be maximally effective. After symptoms are controlled, treatment is continued for 1–2 years to prevent relapse. In patients with multiple psychotic episodes, treatment may be required for many years.

Psychological Treatment

- General support for the patient and his or her family and family education.
- Cognitive behavioral therapy may help patients to cope with their symptoms and also to adhere to treatment with antipsychotic drugs.

Social Treatment

- After symptoms of schizophrenia have been controlled by drugs, social and occupational rehabilitation is required to obtain employment and to re-establish a social network.

Q. Classify anxiety disorders. Discuss briefly the clinical features and management of anxiety disorders.

Q. Generalized anxiety disorder.

Q. Phobic disorder.

Q. Panic disorder.

Q. Obsessive-compulsive disorder.

Classification of Anxiety Disorders as Per DSM-5

- Anxiety disorders (panic disorder, generalized anxiety disorder, phobia, etc.)
- Obsessive-compulsive and other related disorders
- Trauma- and stressor-related disorders (post-traumatic stress disorder, acute stress disorder, adjustment disorder, etc.)

Generalized Anxiety Disorder

- Generalized anxiety disorder is characterized by excessive worry and anxiety that are difficult to control and cause significant distress and impairment. This is the most common clinically significant anxiety disorder.

Clinical Features

- Initial manifestations appear at the age of 20–35 years, and it is more common in women.
- Symptoms include excessive anxiety and worry about a number of events or activities, irritability, difficulty in concentrating, and insomnia for at least six months. Somatic manifestations include cardiac (tachycardia, increased BP), gastrointestinal (e.g. dyspepsia, bowel disturbance), and neurological symptoms (e.g. headache, near-syncope).
- Many physical illnesses like hyperthyroidism, pheochromocytoma, hypoglycemia and alcohol withdrawal can mimic anxiety disorders. Hence, these conditions should be ruled out before making a diagnosis of generalized anxiety disorder.

Treatment

- Antidepressants such as escitalopram and venlafaxine are effective in anxiety disorder. Other useful drugs are benzodiazepines and buspirone.
- Psychotherapy (cognitive-behavioral therapy), relaxation and biofeedback may be of some help.

Phobic Disorder

- A phobia is an abnormal or excessive fear of an object or situation, which leads to avoidance of it.

- *Social phobia* is marked and persistent fear of social or performance situations such as attending social functions, dating, participation in small groups, etc. They often live alone and work at solitary jobs.
- *Agoraphobia* is fear of open places. Agoraphobic patients fear venturing into strange and distant areas. They also fear being in crowds, standing in line, or using public transport.
- *Claustrophobia*—this is opposite of agoraphobia, i.e. fear of closed spaces. For example, fear of MRI when head goes into the MRI machine.
- There are several other types of specific phobias, some of which are acrophobia (fear of heights), aviophobia (fear of flying), trypanophobia (fear of injections), zoophobia (fear of animals, usually spiders, snakes, or mice), etc.

Treatment

- *Exposure therapy*: Patients are encouraged to seek out, confront, and remain in contact with what they fear until their anxiety is gradually relieved through a process called habituation.
- Benzodiazepines (lorazepam) or β blockers (propranolol) are helpful to prevent phobia if taken before getting exposed to the object of fear.

Panic Attack and Panic Disorder

- Panic attack is the sudden onset of a brief period of intense discomfort, anxiety, or fear accompanied by somatic symptoms. Panic disorder is occurrence of repeated panic attacks accompanied by fears about future attacks or changes in behavior to avoid situations that might predispose to attacks.
- Somatic symptoms include chest pain, palpitations, dizziness, nausea and carpopedal spasm. These symptoms are in part due to involuntary over-breathing (hyperventilation). Patients often fear they are suffering from a serious illness such as a heart attack or stroke, and may seek emergency medical care.
- Panic attacks may occur in any anxiety disorder (such as phobias). For example, a person with a phobia of snakes may panic at seeing a snake.

Treatment

- Antidepressants such as sertraline, amitriptyline, etc. are effective. Benzodiazepines work more rapidly than antidepressants, but there is risk of dependence if used for long time.
- Psychotherapy in the form of exposure therapy and cognitive-behavioral therapy are used along with drugs.

Obsessive-compulsive Disorder (OCD)

- Obsessions are persistent intrusive thoughts. Compulsions are intrusive behaviors. In the obsessive-compulsive reaction, an irrational idea or impulse persistently intrudes into the mind, leading to repetitive actions (such as washing the hands many times). These actions are recognized by the individual as absurd, but anxiety is alleviated only by ritualistic performance of the action. Under extreme stress, these patients may exhibit paranoid and delusional behaviors, which can mimic schizophrenia.
- These patients are usually predictable, orderly, and intelligent. Highest prevalence is in the young, divorced, separated, and unemployed. Males and females are equally affected.
- There is a high correlation between OCD and depression; two-thirds of OCD patients will develop major depression during their lifetime.

Treatment

- Exposure and ritual prevention therapy is often effective; it involves gradually exposing patients to situations or people that trigger obsessions and rituals while requiring them not to perform their rituals.
- Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and clomipramine are also effective in OCD.

Q. Post-traumatic stress disorder (PTSD).

- PTSD is recurring, intrusive recollections of an overwhelming traumatic event (e.g. rape, severe burns, accident, military combat). Recollections last >1 month and begin within 6 months of the event.
- Women are more affected than men.

Etiology and Pathophysiology

- It is hypothesized that in PTSD there is excessive release of norepinephrine from the locus coeruleus in response to stress and increased noradrenergic activity at projection sites in the hippocampus and amygdala. These changes facilitate the encoding of fear-based memories.
- Risk factors for the development of PTSD include a past psychiatric history and personality characteristics of high neuroticism and extroversion. Twin studies show a substantial genetic influence.

Clinical Features

- PTSD usually starts after a few days or months after the traumatic event. Generally, events likely to evoke PTSD are those that invoke feelings of fear, helplessness, or horror.

- Typical symptoms are recurrent intrusive memories (flashbacks) of the traumatic event, as well as sleep disturbance, nightmares (usually of the traumatic event) from which the patient awakes in a state of anxiety, symptoms of autonomic arousal, and emotional blunting. Patients often actively avoid stimuli that precipitate recollections of the trauma.
- These patients are at risk of developing other disorders related to anxiety, mood, and substance abuse.

Treatment

- *Psychotherapy*: Involves exposure therapy. Here the person is exposed to situations which he avoids because they may trigger recollections of the trauma. Repeated exposure in fantasy to the traumatic experience itself usually lessens distress after some initial increase in discomfort.
- Selective serotonin reuptake inhibitors (SSRIs) such as sertraline are also effective in PTSD.
- Most patients recover within 2 years.

Q. What are mood disorders (affective disorders)? Discuss the etiology, clinical features, diagnosis, and management of depression.

- Mood disorders are emotional disturbances consisting of prolonged periods of excessive sadness, excessive joyousness, or both. They include depression, bipolar disorder (combining episodes of both mania and depression) and dysthymia.

Depression

- Depression is characterized by persistent low mood and loss of interests/pleasure. Prolonged depression is called dysthymia.
- Depression may be mild, moderate or severe, and episodic, recurrent or chronic. It can be both a complication of a medical condition or can be a cause of medical condition.

Etiology

- Genetic predisposition.
- Adverse life events and emotional deprivation early in life.
- Hypofunction of monoamine neurotransmitter systems (5-HT and noradrenaline).
- Abnormal hypothalamo-pituitary-adrenal axis (HPA) regulation, which results in elevated cortisol levels that do not suppress with dexamethasone.
- Medical conditions causing/predisposing depression: Hypothyroidism, severe anemia, hyperparathyroidism, Cushing's disease, Addison's disease, tuberculosis, HIV, dementia, post-traumatic brain injury syndromes, malignancy, SLE, etc.
- Drugs: Alcohol, beta blockers, withdrawal from cocaine and amphetamines.

Diagnosis

- For diagnosis, ≥5 of the following must have been present nearly everyday during the same 2-week period, and one of them must be depressed mood or loss of interest or pleasure:
  - Depressed mood most of the day
  - Markedly diminished interest or pleasure in all or almost all activities for most of the day
  - Significant (>5%) weight gain or loss or decreased or increased appetite
  - Insomnia (often sleep-maintenance insomnia) or hypersomnia
  - Psychomotor agitation or retardation observed by others (not self-reported)
  - Fatigue or loss of energy
  - Feelings of worthlessness or excessive or inappropriate guilt
  - Diminished ability to think or concentrate or indecisiveness
  - Recurrent thoughts of death or suicide, a suicide attempt, or a specific plan for committing suicide

Investigations

- Diagnosis is mainly based on clinical criteria. However, investigations are useful to exclude physical conditions that can cause depression.
- Tests include CBC, TSH levels, and routine electrolyte, vitamin B_{12}, and folate levels.
- Testing for illicit drug use if suspected.

Management

Antidepressants

- *Tricyclic antidepressants (TCAs)*: They inhibit the reuptake of noradrenaline and 5-HT at synaptic clefts. Their main side-effects are anticholinergic effects, postural hypotension and cardiotoxicity. Examples are imipramine and amitriptyline.
- *Monoamine oxidase inhibitors (MAOIs)*: These drugs inhibit the metabolism of noradrenaline (norepinephrine) and 5-HT. They are rarely used now because of side effects like hypertensive crisis when given along with tyramine containing foods. Examples are phenelzine and selegiline. Moclobemide is a selective inhibitor of monoamine oxidase subtype A, which is less likely to cause hypertensive crisis.
- *Selective serotonin reuptake inhibitors (SSRIs)*: They have less anticholinergic effects, are less cardiotoxic, and

cause less sedation. Examples are citalopram, escitalopram, fluoxetine, sertraline and paroxetine.

- *Serotonin-norepinephrine reuptake inhibitors (SNRIs)*: these are venlafaxine, and duloxetine.
- *Melatonergic antidepressant*: Agomelatine is a melatonergic (MT1/MT2) agonist and a 5-HT2c receptor antagonist. It is used for major depressive episodes. It has fewer adverse effects than most antidepressants and does not cause daytime sedation.
- *Others*, e.g. mirtazepine.
- Almost all the antidepressants are equally effective, but newer agents have fewer side effects. Improvement may take 2–4 weeks.

Psychological treatments

- Both cognitive behavioral therapy and interpersonal therapy are as effective as antidepressants for mild to moderate depression.

Electroconvulsive therapy (ECT)

- May be required for severe depression complicated by psychosis, or suicidal risk.

Q. Cyclothymic disorder.

- This is characterized by hypomanic and mini-depressive periods that last a few days, follow an irregular course, and are less severe than those in bipolar disorder. It may progress to bipolar dosiorder. Symptoms must occur for more than half the days during a period of ≥ 2 yr.

Treatment

- Supportive care.
- Sometimes a mood stabilizer (lithium, valproate, carbamazepine).

Q. Bipolar disorder (manic depression).

- Bipolar disorders are characterized by episodes of mania and depression, which may alternate, although many patients have a predominance of one or the other.

Etiology

- *Genetic factors*—bipolar disorder is strongly heritable.
- There is also evidence of dysregulation of serotonin and norepinephrine.
- Stressful life events and physical illness may trigger the episodes.
- Drugs (e.g. cocaine, amphetamines), alcohol, and certain antidepressants (e.g. tricyclics, MAOIs) may play a role in triggering episodes.

Clinical Features

Manic Episodes

- Abnormally and persistently elevated mood lasting for at least one week.
- Inflated self-esteem or grandiosity.
- Decreased need for sleep.
- More talkative than usual.
- Racing thoughts or flight of ideas.
- Distractibility.
- Increase in goal-directed activity.
- Excessive involvement in pleasurable activities such as spending money or sexual indiscretion.
- Hypomania refers to a briefer duration of manic symptoms (at least four days), and is often used to refer to a less severe level of symptoms.

Depressive Episodes

- Depression is characterized by features described under depression.

Investigations

- These are done to rule out hyperthyroidism and stimulant drug abuse which can mimic bipolar disorder.

Management

- Drugs for bipolar disorder include mood stabilizers and second-generation antipsychotics.
- Mood stabilizers include lithium, sodium valproate, and lamotrigine. Second-generation antipsychotics include aripiprazole, lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone.
- Antidepressants (e.g. SSRIs) are sometimes added for severe depression, but they are not recommended as sole therapy for depressive episodes.
- Electroconvulsive therapy (ECT) is sometimes used for depression refractory to treatment and is also effective for mania.

Q. Anorexia nervosa.

Definition

- Anorexia nervosa is an eating disorder characterized by the following features:
  - Refusal to maintain weight within normal range.
  - Fear of weight gain.
  - Distortion of body image so that patients regard themselves as fat even when grossly underweight.

Clinical Features

- It is common in women.

- Patients usually avoid high calorie foods leading to significant weight loss. Some patients may eat and use purging to control their weight (through self-induced vomiting, use of laxatives and diuretics).
- Associated anxiety and depressive symptoms are common. Downy hair (lanugo) may develop on the back, forearms and cheeks. Extreme starvation may affect multiple organ systems, especially heart and skeletal system. Amenorrhea is also common.

Etiology

- Exact etiology is unknown, but a combination of psychological, biological, family, genetic, environmental, and social factors play a role.
- Social pressure on women to be thin also plays a role.

Investigations

- Rule out other causes of weight loss such as malabsorption syndromes (e.g. due to inflammatory bowel disease or celiac disease), new-onset type 1 diabetes, adrenal insufficiency, and cancer. Amphetamine abuse may cause similar symptoms.

Management

- All other causes of weight loss should be ruled out (e.g. malabsorption, cancer, etc.).
- The goals of treatment are: To ensure patient's physical well-being, to maintain normal body weight, and to correct the psychological disturbances.
- Patients can be treated on outpatient basis. Admission is required if there is severe weight loss or if there is a risk of death from medical complications or from suicide.
- Cognitive behavioral therapy helps the patient manage the anxiety related to eating and poor body image by developing more adaptive thoughts and coping strategies. Family therapy encourages family members to refeed patients at home with the support of a family therapist.
- Psychotropic drugs are helpful if there is associated depression.

Q. Bulimia nervosa.

- Bulimia nervosa is characterized by episodes of binge eating, followed by compensatory behavior of the purging type (self-induced vomiting, laxative abuse, diuretic abuse) or nonpurging type (excessive exercise, fasting, or strict diets).
- Binge eating disorder is different from bulimia nervosa. Binge eating disorder is characterized by recurrent episodes of consuming large amounts of food without any compensatory behavior.

Clinical Features

- It is more common in women and the etiology is same as anorexia nervosa.
- Patients typically describe binge-purge behavior. Binges involve rapid consumption of large amounts of high calorie foods. Binge eating episodes can occur several times a day and triggered by psychological stress. Binge eating is followed by compensatory behaviors: Self-induced vomiting, use of laxatives or diuretics, excessive exercise, and/or fasting.
- There is dissatisfaction with body shape and weight but weight is maintained within normal limits (note that in anorexia nervosa there is significant weight loss).
- Physical signs of repeated self-induced vomiting include pitted teeth (from gastric acid), calluses on knuckles and parotid gland enlargement.

Management

- Cognitive behavioural therapy.
- *Drugs*: Antidepressants like fluoxetine, amitriptyline have been shown to reduce binge eating. Other helpful drugs are topiramate and ondansetron.

Q. What are somatic symptom disorders?

- Somatic symptom disorders (earlier called somatoform disorders) are characterized by multiple persistent physical complaints associated with excessive and maladaptive thoughts, feelings, and behaviors related to those symptoms.
- Somatic symptom disorders include the following:
  - Somatic symptom disorder
  - Conversion disorder
  - Psychological factors affecting a medical condition
  - Factitious disorder
  - Other specific and nonspecific somatic symptom disorders.

Etiology

- Exact cause is unknown.
- Contributory factors include depression or anxiety, erroneous interpretation of somatic symptoms as evidence of disease, and preoccupation with physical illness.
- Family history or previous history of a particular condition may provoke concerns about illness.

Clinical Features

- Physical complaints usually begin before age 30. Most patients have multiple somatic symptoms such as pain, headache, etc. The somatic symptoms are not explained by a medical condition and are also not part of depressive

or anxiety disorder. Physical symptoms may involve one or more organ systems and are not intentional. Symptoms persist for a long time. The symptoms themselves or excessive worry about them is distressing or disrupts daily life. Some patients become overtly depressed.

- When physical complaints accompany another medical disorder, patients overrespond to the implications of the medical disorder; for example, patients who have had an MI may constantly worry about having another MI or think themselves as unfit. Such patients are very anxious about their health problems and are difficult to reassure.
- Whatever the manifestations, the essence of somatic symptom disorder is the patient's excessive or maladaptive thoughts, feelings, or behaviors in response to the symptoms.

Treatment

- Cognitive-behavioral therapy.
- Treatment of concurrent mental disorders (e.g. depression).

Q. Conversion disorder (hysteria; dissociative disorder).

- Conversion disorder consists of neurologic symptoms or deficits that develop unconsciously and non-volitionally without a definable organic cause.
- "Conversion" is characterized by conversion of psychic conflict into physical symptoms. The coping mechanisms used in this condition are repression (a barring from consciousness) and isolation (a splitting of the affect from the idea).

Clinical Features

- It is more common in young and uneducated women from lower socioeconomic class.
- Symptoms often develop abruptly, and onset can often be linked to a stressful event. Patients may present with impaired coordination or balance, weakness, paralysis of an arm or a leg, loss of sensation in a body part, seizures, unresponsiveness, blindness, double vision, deafness, aphonia, difficulty swallowing, sensation of a lump in the throat, or urinary retention. The manifestations are not in the conscious control of the patient.
- There is apparent unconcern (la belle indifference) even in the face of gross physical disability.
- Clues pointing towards conversion disorder are: History of similar episode in the past, presence of a serious precipitating emotional event, presence of associated depression, etc., temporal correlation between the precipitating event and the symptom, and a temporary "solving of the problem" by the conversion.
- A complete physical and neurological examination is important to rule out physical causes.

Treatment

- Reassurance
- Explanation of the cause of symptoms. It is helpful to explain the physiological mechanism for the symptom that emphasizes the link with psychological factors such as stress.
- Advice on how to cope with stress and relaxation techniques.
- Antidepressant drugs are helpful even if the patient is not depressed.
- Cognitive behavioral therapy and other psychological treatments are helpful.

Q. Factitious disorder imposed on self (Munchausen syndrome).

- Factitious disorder imposed on self is a psychiatric disorder in which patients deliberately produce or falsify symptoms and/or signs of illness for the purpose of assuming the sick role. It is also known as Munchausen syndrome named after German Baron Freiherr von Munchausen, who told fanciful tales only to entertain others.
- Factitious disorder may also be imposed on another person (factitious disorder by proxy). This is typically done by caregivers to someone in their care such as a child.
- Patients with factitious disorders differ from malingerers because, there are no obvious external incentives (e.g. economic gain) for their behavior. It is unclear what they gain beyond medical attention for their suffering.

Clinical Features

- Approximately two-thirds of patients with Munchausen syndrome are male. They are usually older with a solitary lifestyle.
- They present frequently with dramatic symptoms. Examination may show previous multiple surgical scars. They often present at night when junior doctors and residents are on duty. The history can be convincing enough to persuade doctors to undertake investigations or initiate treatment, including exploratory surgery.

Management

- Management is by gentle but firm confrontation with clear evidence of the fabrication of illness, together with an offer of psychological support. Any underlying psychological disorders (anxiety, depression) should be treated.

Q. Substance abuse.

- Substance abuse refers to excess or harmful use of a substance despite social, health and occupational problems.
- Substance dependence (addiction) refers to substance abuse associated with psychological dependence (craving), physiologic dependence (withdrawal symptoms on stopping the drug) and tolerance.
- Substance abuse and dependence are major problems worldwide. They affect all races, and all socioeconomic strata. They are more common in men than in women although the gap is narrowing.

Etiology

- Cultural pressures, particularly within a peer group.
- Easy availability of a drug.
- Medical over-prescribing.
- Psychiatric problems such as depression.

Diagnosis

- History.
- Physical examination—needle marks in IV drug users; evidence of localized or systemic infections; staining of teeth, respiratory problems in inhalation drug abuse.
- Drug screening of samples of urine or blood.

Management

- Psychological counseling.
- Harm minimization—for example, advice to use clean needles.
- Substitute prescribing (example methadone in opiate dependence).
- Identifying and treating problems associated with the drug misuse.
- Treatment of complications of drug misuse.

Table 12.1 Commonly abused drugs

Sedatives Benzodiazepines Opiates (morphine, heroin) Barbiturates	• These agents lead to physical dependence • Acute overdose leads to slurred speech, incoordination, unsteady gait, impaired attention or memory, stupor or coma. Psychiatric manifestations include inappropriate behavior, labile mood, impaired judgment and social functioning. Physical signs include nystagmus and decreased reflexes. Death may occur due to respiratory depression • Intravenous drug abusers may develop infections such as hepatitis B, hepatitis C and HIV through needle contamination • Withdrawal from opiates causes intense craving, rhinorrhea, lacrimation, shivering, piloerection, vomiting, diarrhea, tachycardia, hypertension, pupilary dilatation and seizures • Withdrawal from benzodiazepines causes anxiety, hyperactivity, hallucinations, seizures, ataxia and paranoid delusions
Stimulants Amphetamines Cocaine	• They can cause cardiac and cerebrovascular complications through vasopressor effects. Psychiatric disturbances are seen with prolonged use. They do not cause physical dependence • Withdrawal causes a rebound lowering in mood and can cause intense craving. • Chronic amphetamine abuse can cause a syndrome identical to paranoid schizophrenia • Cocaine intoxication can cause toxic psychosis and tactile hallucinations
Hallucinogens Cannabis (ganja) Ecstasy (methylenedioxy-methamphetamine—MDMA) Lysergic acid diethylamide (LSD, also called acid) Psilocybin (magic mushrooms)	• They cause changes in mood and prominent sensory experiences. Confusion and psychotic episodes are common after heavy consumption • Prolonged heavy use increases the risk of developing schizophrenia • Flashback experiences where previous hallucinogen experiences are re-experienced unexpectedly can occur after prolonged use of hallucinogens
Organic solvents Glue Paint thinners	• Solvent inhalation (glue sniffing) is popular in some adolescent groups. • Solvents produce acute intoxication characterized by euphoria, excitement, dizziness and a floating sensation. Further inhalation leads to loss of consciousness • The most severe consequence is hypoxia or anoxia which can cause death

Q. Alcohol dependence.

Q. Complications of chronic alcohol misuse.

Definitions

At-risk Drinking

- >14 drinks/week or 4 drinks per occasion for men
- >7 drinks/week or 3 drinks per occasion for women
- These amounts are associated with increased risk of a wide variety of medical and psychosocial complications.

Alcohol Abuse

Refers to a maladaptive pattern of episodic drinking that results in failure to fulfill obligations, drinking in physically hazardous situations (e.g. driving, boating), legal problems, or social and interpersonal problems without evidence of dependence.

Alcohol Dependence (Alcoholism)

Refers to frequent consumption of large amounts of alcohol with ≥3 of the following:

- Tolerance to the effects of alcohol
- Withdrawal symptoms
- Drinking larger amounts or over a longer period than intended
- Persistent desire or unsuccessful efforts to reduce use without success
- Spending significant time obtaining, using, or recovering from the alcohol
- Important social, occupational, or recreational activities are given up or reduced because of drinking
- Continued use despite physical or psychologic problems

Etiology of Alcohol Dependence

- Availability of alcohol and social patterns of use.
- Genetic factors.
- As a measure to relieve anxiety or depression.
- Many who abuse alcohol have certain personality traits: Feelings of isolation, loneliness, shyness, depression, dependency, hostile and self-destructive impulsivity, and sexual immaturity.
- Social problems: Broken home, disturbed relationship with their family.

Complications of Alcohol Misuse

Acute intoxication
- Emotional and behavioral disturbance, hypoglycemia, aspiration, respiratory depression and even death.

Nervous system
- Peripheral neuropathy, cerebellar degeneration, cerebral hemorrhage, Wernicke's encephalopathy, dementia.

Liver
- Alcoholic liver disease (hepatitis, fatty liver and cirrhosis), liver cancer.

GIT
- Esophagitis, gastritis, pancreatitis, esophageal cancer, Mallory-Weiss syndrome.

RS
- Pulmonary TB, pneumonia.

CVS
- Cardiomyopathy, hypertension.

Skin
- Spider nevi, palmar erythema, Dupuytren's contractures, telangiectasiae.

Musculoskeletal
- Myopathy, fractures.

Endocrine and metabolic
- Pseudo-Cushing's syndrome, hypoglycemia, gout

Reproductive
- Hypogonadism, fetal alcohol syndrome, infertility

Psychiatric problems
- Depression, anxiety, alcohol withdrawal, alcoholic hallucinosis, alcoholic 'blackouts'.

Management

- Advice about the harmful effects of alcohol and safe levels of consumption.
- Disulfiram (200–400 mg daily) can be given to create hatred towards alcohol. It blocks the metabolism of alcohol, causing acetaldehyde to accumulate. When alcohol is consumed, an unpleasant reaction follows with headache, flushing and nausea. Disulfiram should be used along with other treatments, especially supportive psychotherapy.
- Acamprosate (333–666 mg orally three times daily) is used to reduce craving, for maintenance of abstinence, and can be continued even during periods of relapse.
- Naltrexone (opiate antagonist) lowers relapse rates after cessation of drinking by lessening the pleasurable effects of alcohol. It also reduces craving for alcohol.
- Supportive psychotherapy.

Q. Alcohol withdrawal syndrome.

- Alcohol is a CNS depressant, hence, withdrawal symptoms are caused by its rapid withdrawal due to unmasking of compensatory over-activity of certain parts of the nervous system, including sympathetic autonomic outflow.

Pathophysiology

- Alcohol withdrawal causes a functional decrease in the inhibitory neurotransmitter GABA. This leads to increased activity of excitatory neurotransmitters such as norepinephrine, glutamate, and dopamine.

- Alcohol also acts as an NMDA receptor antagonist. Withdrawal leads to increased activity of these excitatory neuroreceptors, resulting in tremors, agitation, hallucinations, seizures, tachycardia, hyperthermia, and hypertension.

Clinical Features

- Symptoms usually occur within eight hours of stopping alcohol, reach a peak on the 2nd or 3rd day, and diminish by the 4th or 5th day.
- Symptoms include anxiety, tremor, insomnia, decreased cognition, irritability, headache, diaphoresis, palpitations, and in severe cases delirium tremens.
- Delirium tremens (DTs) is the most severe form of alcohol withdrawal manifested by altered mental status (global confusion) and sympathetic hyperactivity, which can progress to cardiovascular collapse. It is characterized by mental confusion, visual hallucinations (often of snakes, bugs, etc.), agitation, tremor, tachycardia, diaphoresis, dehydration, and seizures.

Investigations

- Rule out hepatic encephalopathy, gastrointestinal bleeding, cardiac arrhythmia, infection, and glucose or electrolyte imbalance by appropriate tests.
- CT or MRI of brain may be required to rule out intracranial pathology.

Treatment

- *Benzodiazepines*—diazepam or chlordiazepoxide are commonly used, but other agents can also be used. Benzodiazepines exert their effect via stimulation of gamma-aminobutyric acid (GABA) receptors, causing a decrease in neuronal activity and relative sedation. They alleviate most symptoms of withdrawal. The average patient requires 25–50 mg of chlordiazepoxide or 10 mg of diazepam given PO every 4–6 hour on the first day and then tapered off over a period of 3–5 days. Oral therapy is enough in most cases, but parenteral therapy may be required in severe cases associated with delirium tremens and seizures.
- Thiamine supplementation should be give to all patients.

Q. Complications of smoking.

Q. Management of smoking cessation (nicotine addiction).

- Cigarette smoking is a major preventable cause of disease worldwide.
- Cigarette smoke contains more than 4000 substances. The main active ingredient is nicotine. Other important substances include carbon monoxide, tar, aromatic hydrocarbons, benzopyrine, nitrosamine, vinyl chloride, trace metals, phenol, cresol and catechol. Most of these are carcinogens.

Passive Smoking

- Passive smoking (secondhand smoke) refers to involuntary exposure of nonsmokers to tobacco smoke from the smoking of others. Passive smoking is a mixture of sidestream smoke given off by the burning cigarette and of mainstream smoke that is exhaled by the smoker. Sidestream smoke, generated under the lower temperature conditions in the smoldering cigarette, has higher concentrations of many of the toxic compounds than the mainstream smoke.
- Passive smoking is also associated with all the complications of active smoking.

Effects of Nicotine

- Nicotine is a sympathomimetic. It causes increase in both systolic and diastolic blood pressures, tachycardia, peripheral vasoconstriction, and increases myocardial oxygen demand. CNS effects are mediated through central nicotinic cholinergic receptors and include increased arousal and alertness. Nicotine releases beta-endorphin in the CNS and has other endocrinological effects. Acute intoxication causes nausea, salivation, pallor, weakness, abdominal pain, vomiting or diarrhea, dizziness, headache, confusion, various sensory disturbances, tachycardia and hypertension.
- Acute withdrawal of nicotine causes dysphoric mood, insomnia, irritability, anxiety, restlessness, increased appetite, difficulty to concentrating and craving for nicotine.

Complications of Chronic Smoking

CVS
- Increased risk of angina and MI
- Hypertension
- Aortic aneurysm
- Peripheral vascular disease

RS
- Increased incidence of respiratory tract infections
- COPD
- Laryngeal cancer
- Lung cancer

GIT
- Periodontitis
- Discoloration of teeth, reduced taste and smell.
- Acid peptic disease
- Increased risk of cancers of oral cavity, esophagus, stomach, colon and pancreas

Nervous system
- Irritability
- Increased risk of stroke

Genitourinary system
- Impotence
- Infertility
- IUGR
- Increased risk of spontaneous abortion, fetal death and sudden infant death
- Cancer of urinary bladder

Blood
- Polycythemia

Management of Smoking Cessation

Behavioral Therapy

- These include individual and group counseling regarding the bad effects of smoking, ways to quit smoking, etc. Abrupt cessation, particularly on a defined "quit day", is the preferred strategy instead of gradual tapering.

Nicotine Replacement Therapy

- Nicotine replacement therapy ameliorates withdrawal symptoms of smoking cessation. However, many smokers can quit smoking even without nicotine replacement.
- Nicotine is available for use in many forms: Chewing gum or lozenge, transdermal patch, nasal spray, and inhaler. All are equally effective. Patient takes one of these preparations whenever there is urge to smoke. Gradually replacement therapy is also withdrawn.

Bupropion

- This is an antidepressant and doubles the chances of smoking cessation. Exact mechanism of action is not known. It can be given at a dose of 150 mg up to 1 year.

Varenicline

- Varenicline is a partial agonist of nicotinic acetylcholine receptors. It has shown good results for smoking cessation.

Q. What are the sleep disorders?

Q. Discuss the causes and management of insomnia.

- *Sleep consists of two pahses*: (1) REM (rapid eye movement) sleep, also called dream sleep, and (2) NREM (non-REM) sleep. NREM sleep is divided into stages 1, 2, 3, and 4 which can be recognized by different EEG patterns. Stages 3 and 4 are "delta" or deep sleep. Dreaming occurs mostly in REM sleep.
- Sleep is a cyclic phenomenon, with REM and NREM sleep alternating throughout the night. Stage 3 and 4 sleep decreases as the age advances.

Sleep disorders can be divided into 2 broad categories:
- *Parasomnias*—These are unusual experiences or behaviors that occur during sleep; they are sleep terror, sleepwalking and nightmare disorder.
- *Dyssomnias*—These are characterized by abnormalities in the amount, quality, or timing of sleep; they are insomnia and hypersomnia, narcolepsy, and circadian rhythm sleep disorder.

Insomnia

- Insomnia is characterized by an inadequate quantity or quality of sleep.
- Affected patients complain of difficulty initiating or maintaining sleep, resulting in non-restorative sleep and impairment of daytime functioning.

Causes

Transient insomnia
- Change of sleeping environment
- Jet lag
- Changes in work shift
- physical discomfort (excessive noise, unpleasant room temperature)
- Stressful life events (e.g. loss of a loved one, divorce, loss of employment, preparing to take an examination)
- Acute medical or surgical illnesses
- Stimulant medications (theophylline, quinolones, caffeine)

Chronic insomnia
- Depression
- Mania
- Abuse of alcohol
- Heavy smoking
- Neurological disorders (fatal familial insomnia, Alzheimer's disease, Parkinson's disease, cerebral hemispheric and brainstem strokes, brain tumors)
- Chronic medical disorders (COPD, CCF, AIDS)
- Primary sleep disorders (restless legs syndrome, sleep apnea)

Evaluation

History

- Duration of symptoms and history of any events (e.g. work change, new drug, new medical disorder) that coincided with onset.
- Determine the quality and quantity of sleep by asking: Time of going to bed, latency of sleep (time from bedtime to falling asleep), number and time of awakenings, final morning awakening and arising times, frequency and duration of naps.

- Ask about bedtime events (e.g. food or alcohol consumption, physical or mental activity).
- History of snoring, interrupted breathing patterns, and other nocturnal respiratory disturbances suggest sleep apnea syndromes.
- History of depression, anxiety, mania, and hypomania suggest mental sleep disorders.
- Ask about any medical disorders that can interfere with sleep, including COPD, asthma, heart failure, hyperthyroidism, gastroesophageal reflux, neurologic disorders (particularly movement and degenerative disorders), and painful disorders (e.g. rheumatoid arthritis).
- Ask about any drug intake that could interfere with sleep (e.g. SSRIs, phenytoin, amphetamines, aminophyline).

Physical Examination

- Look for any upper respiratory tract abnormalities that can cause obstructive sleep apnea and snoring.
- Look for evidence of diseases that could interfere with sleep.

Investigations

- Appropriate tests to rule out any medical disorder that can cause insomnia.

Management

- *Good sleep hygiene*—go to bed only when sleepy, get up early, discontinue caffeine and nicotine, daily exercise, avoid alcohol, and practice relaxation techniques.
- *Pharmacologic measures*—hypnotic medications such as lorazepam (0.5 mg at night), zolpidem (5–10 mg at bedtime), and zaleplon (5–10 mg at bedtime). In general, medications should be used for short courses of 1–2 weeks. Melatonin (a hormone secreted by pineal gland) is effective for delayed sleep onset. Suvorexant is a new treatment for insomnia that acts by blocking brain orexin receptors, thereby blocking orexin-induced wakefulness signals and enabling sleep initiation. Tasimelteon, a melatonin receptor agonist, can increase nighttime sleep duration and decrease daytime sleep duration.
- Treatment of underlying cause—such as COPD, CCF, etc.

Q. Narcolepsy.

- Narcolepsy is characterized by chronic excessive daytime sleepiness, often with sudden loss of muscle tone (cataplexy).

Etiology

- Narcolepsy features dysregulation of the timing and control of REM sleep. Therefore, REM sleep intrudes into wakefulness and into the transition from wakefulness to sleep.
- *Genetic factors*: Narcolepsy is strongly associated with specific HLA haplotypes, and children of patients with narcolepsy have increased risk.
- Deficiency of neuropeptide hypocretin-1 is found in CSF of narcoleptic animals and human patients.

Clinical Features

- The disease typically begins in the teens and early twenties, affects both sexes equally, and usually levels off in severity at about 30 years of age.
- Narcolepsy is characterized by the following features:
  - *Daytime sleepiness*—sudden and brief attacks of sleep during any type of activity.
  - *Cataplexy*—sudden loss of muscle tone which may cause the person to slump to the floor or unable to move.
  - *Sleep paralysis* is a complete inability to move for one or two minutes immediately after awakening.
  - *Hypnagogic hallucinations*—visual or auditory, occur just as the patient is falling asleep or upon awakening.
- Diagnosis can be confirmed by polysomnography and multiple sleep latency testing.

Treatment

- Modafinil, a non-amphetamine wakefulness promoting agent has become a first line agent because of less abuse potential.
- CNS stimulant drugs such as methylphenidate or amphetamine derivatives are used instead of or with modafinil if patients do not respond to modafinil.
- Tricyclic antidepressants (clomipramine) and SSRIs may be useful for cataplexy, sleep paralysis, and hypnagogic and hypnopompic hallucinations.

Q. Sleep terror.

Q. Nightmares.

- Sleep terror is an abrupt, terrifying arousal from sleep. It occurs in stage 3 or stage 4 sleep.
- It usually occurs in preadolescent boys although it may occur in adults as well.
- Symptoms are fear, sweating, tachycardia, and confusion for several minutes, and the event is not remembered on awakening.
- Treatment is with benzodiazepines (e.g. diazepam, 5–10 mg at bedtime), since it will suppress stage 3 and stage 4 sleep.
- Nightmares occur during REM sleep and cause full arousal, with intact memory for the unpleasant episode.

Q. Sleepwalking (somnambulism).

- Sleepwalking also known as somnambulism involves getting up and walking around or performing a complex motor activity while in a state of sleep.
- It generally occurs in deep nonrapid eye movement (NREM) (stages 3 and 4) sleep.

Causes

- Somnambulism may be precipitated by a variety of conditions such as insufficient sleep resulting from an irregular sleep schedule, staying up late, giving up a daily nap or waking early in the morning.
- In elderly, it may be a feature of dementia.
- Drugs (phenothiazines, chloral hydrate, lithium), marijuana, alcohol and medical conditions (e.g. complex partial seizures) can also cause sleepwalking.
- It may be familial.

Clinical Features

- It affects mostly children aged 6–12 years. Patients with this disorder carry out automatic motor activities during sleep that range from simple to complex. There is no memory of the event. Individuals may walk, urinate inappropriately, eat, or exit from the house while remaining only partially aware. Attempt to awaken them may rarely lead to agitation or even violence.

Treatment

- Reassurance is the mainstay of treatment. Patients and parents should be told that sleepwalking is benign and eventually disappears.
- Auditory, tactile, and visual stimuli should be avoided early in the sleep cycle as these may induce sleepwalking.
- Parents should be instructed to lock windows and doors, remove obstacles and sharp objects from the room to avoid injuries.
- Low-dose benzodiazepine is the drug of choice if the episodes are very frequent. Tricyclic antidepressants and trazodone are also beneficial.

Q. Electroconvulsive therapy.

- Electroconvulsive therapy (ECT) involves the administration of high-voltage, brief direct current impulses to the head while the patient is anesthetized and paralyzed by muscle relaxants.
- ECT causes a generalized central nervous system seizure (peripheral convulsion is not necessary) by means of electric current. Electrical current insufficient to cause a seizure produces no therapeutic benefit.
- The mechanism of action is not known, but it is thought to involve major neurotransmitter responses at the cell membrane.

Indications for ECT

- Major depression refractory to antidepressants, with psychotic features or suicidal risk.
- Bipolar mood disorder.
- Schizophrenia.
- Organic delusional disorder.
- Obsessive-compulsive disorder.
- Catatonia secondary to medical conditions.

Contraindications

- Increased intracranial pressure.
- Space-occupying intracranial lesion.
- Recent cerebral hemorrhage or stroke.
- Venous thrombosis.
- Unstable or severe cardiovascular disease.
- Bleeding or otherwise unstable vascular aneurysm.
- Severe pulmonary condition.

Side Effects

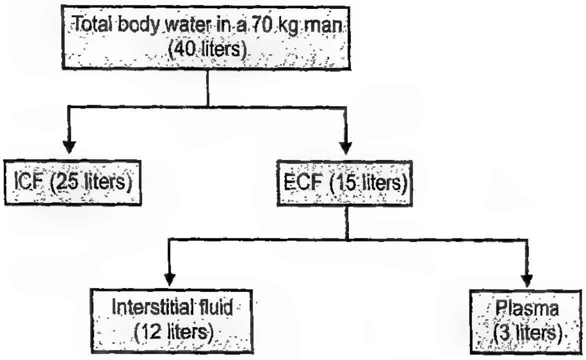
- Memory disturbance.
- Headache.
- Aspiration of gastric contents.

13 Fluid and Electrolyte Disorders

Q. Write briefly about the normal distribution of water and electrolytes in the body.

Normal Distribution of Water in the Body

- In a typical adult male, the total body water (TBW) is approximately 60% of the body weight (i.e. 40 liters in a 70 kg male). Out of this, two-thirds (25 liters) is intracellular fluid (ICF), and one-third (15 liters) is extracellular fluid (ECF). ECF is further divided into interstitial fluid (12 liters) and plasma (3 liters).
- The main difference between the plasma and interstitial fluid is the presence of high concentration of protein in the plasma.



Normal Distribution of Electrolytes in the Body

- The major electrolytes in the body are sodium (Na), potassium (K), chloride (Cl) and bicarbonate (HCO_3). Other important electrolytes are calcium, phosphorus and magnesium.
- Most of the sodium, chloride and bicarbonate are present in the ECF. Most of the potassium and phosphates are present in ICF. The major force maintaining the differences in the distribution of Na and K is sodium-potassium pump which is present in all cell membranes. This difference is important for many cell processes, including the excitability of conducting tissues such as nerve and muscle. High concentration of protein in the plasma favors fluid retention within the capillaries, thus maintaining an adequate circulating plasma volume.

Electrolytes	Normal plasma values
Na^+	135–145 mEq/L
K^+	3.5–5 mEq/L
Cl^-	98–107 mEq/L
HCO_3^-	22–28 mEq/L
Mg	1.6–3 mg/dl
Serum osmolality	285–295 mOsm/kg water
Blood pH	7.36–7.44

Q. Volume depletion (dehydration).

- Volume depletion occurs when fluid is lost from the extracellular fluid at a rate exceeding net intake.

Etiology

- ***Gastrointestinal losses***: Vomiting, diarrhea, bleeding, and external drainage.
- ***Renal losses***: Diuretics, osmotic diuresis, salt wasting nephropathies, hypoaldosteronism.
- ***Skin or respiratory losses***: Insensible losses, sweat, and burns.
- Third-space sequestration: Intestinal obstruction, crush injury, major bone fracture, peritonitis, and acute pancreatitis.

Clinical Features

- Symptoms are easy fatigability, thirst, muscle cramps, postural dizziness, and decreased urine output.
- Examination reveals tachycardia, reduced or absent tears, reduced skin turgor, dry mucous membranes, altered mental status, hypotension and shock.

Laboratory Abnormalities

- Serum sodium concentration may be high when more water loss is lost and may be low in both salt and water loss.
- Blood urea and creatinine may be elevated.

- Urine sodium concentration is less than 25 mEq/L in extrarenal causes of volume depletion, because of sodium retention by the kidneys whereas in renal causes of volume depletion it is more than this.
- Urine osmolality often exceeds 450 mOsml/kg in volume depletion except in osmotic diuresis, administration of diuretics, and diabetes insipidus.
- Hematocrit may be high except when there is blood loss.

Treatment

- Mild to moderate cases can be corrected by oral supplementation of fluids in the form of oral rehydration salt.
- Severe volume depletion requires intravenous hydration using Ringer lactate or normal saline.

Q. Hypervolemia/fluid overload.

Q. Define edema. Discuss the causes, pathophysiology, clinical manifestations, investigations and management of generalized edema.

- Hypervolemia or fluid overload is a condition characterized by excessive fluid volume. It is due to an expansion of the extracellular fluid volume, including the intravascular or interstitial space.

Causes of Fluid Overload

- Sodium retention along with water: Renal failure, nephrotic syndrome, heart failure, cirrhosis, hypoalbuminemia.
- *Iatrogenic*: Excess IV fluids.

Clinical Features

- Volume overload presents as edema and effusions. Mild edema may be detected only by the occurrence of weight gain, whereas overt edema is apparent only after 3 to 4 L of fluid has accumulated.
- Patients may complain of dyspnea because of pulmonary edema. There may be lung crepitations, raised JVP, S_3 gallop, ascites and pleural effusion.

Investigations

- Investigations are usually not required because hypervolemia is primarily a bedside diagnosis.
- Urea, creatinine to rule out renal failure.
- Urine, protein to rule out proteinuria.
- LFT, ECG and echocardiogram to rule out liver and cardiac failure.
- Chest X-ray may show pulmonary edema or pleural effusions.

Treatment

- Treat the underlying cause.
- Reduce sodium and water intake.
- Diuretics are used to increase sodium and water excretion.

Q. Generalized edema.

- Edema is defined as a palpable swelling produced by expansion of the interstitial fluid volume.
- Edema becomes clinically apparent when the interstitial volume has increased by 2.5 to 3 L, an amount that is almost equal to the plasma volume.

Causes

- Heart failure
- Renal failure
- Cirrhosis of liver
- Hypoalbuminemia (nephrotic syndrome, protein-losing enteropathy, malnutrition)
- Hypothyroidism
- Pregnancy and premenstrual edema
- Refeeding edema
- Inflammation or sepsis
- Allergic reactions, including certain forms of angioedema
- *Drugs*: Minoxidil, diazoxide, thiazolidinediones, calcium channel blockers, NSAIDs, fludrocortisone, estrogens

Pathophysiology

- For generalized edema to occur, two factors must be present:
  1. An alteration in capillary hemodynamics that favors the movement of fluid from the vascular space into the interstitium. Such movement requires a change in one or more components of Starling's law: Increased capillary hydrostatic pressure, decreased capillary oncotic pressure, and increased capillary permeability.
  2. Retention of sodium and water by the kidneys. The retention of sodium and water can either be a primary event, as in renal failure, or a secondary event due to reduction in cardiac output (e.g. heart failure) or systemic vascular resistance (e.g. cirrhosis).

Clinical Manifestations

- Peripheral edema manifests as pitting on pressure in dependent areas, i.e. lower limbs in ambulatory patients and sacrum in patients at bed rest. Non-pitting edema is seen in lymphatic obstruction or thyroid disease. Patients with the nephrotic syndrome may also have prominent periorbital edema due to the low tissue pressure in this area.

- Abdominal distension due to ascites. In cirrhosis, ascites is seen first followed by peripheral edema. In cardiac failure, peripheral edema is seen first followed by ascites.
- Dyspnea, orthopnea and bilateral basal lung crepitations due to pulmonary edema. Pleural effusion may be present
- JVP is raised.
- There may be signs of underlying disease.

Investigations

- Hematocrit may be low due to hemodilution.
- Hyponatremia may be present (dilutional hyponatremia) except in cases of primary renal sodium retention.
- Thyroid function tests.
- Serum albumin and liver function tests.
- Renal function tests.
- Urine analysis to look for proteinuria.
- ECG, echocardiogram to rule out cardiac failure.

Management

- Dietary sodium and water restriction (to minimize fluid retention).
- Diuretic therapy—pulmonary edema is life-threatening and requires immediate treatment. In all other conditions, removal of the excess fluid can proceed more slowly. Diuretics like furosemide or torsemide can be given IV in emergencies, otherwise oral therapy is sufficient.
- Treatment of the underlying disorder.

Q. Discuss the etiology, clinical features, investigations and management of hyponatremia.

- Hyponatremia is defined as a serum sodium concentration <135 mEq/L. Normal serum sodium levels are between approximately 135 and 145 mEq/L.
- *Hyponatremia is classified into 3 types based on the ECF volume status*: Euvolemic, hypovolemic, and hypervolemic.

Causes of Hyponatremia

Euvolemic hyponatremia
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)
- Glucocorticoid deficiency
- Hypothyroidism
- Stress
- Drugs (barbiturates, carbamazepine, clofibrate, opioids, vincristine, NSAIDs)

Hypovolemic hyponatremia
- *Integumentary loss*: Sweating, burns
- *Gastrointestinal loss*: Vomiting, diarrhea
- *Renal loss*: Diuretics, osmotic diuresis, salt-wasting nephropathy, mineralocorticoid deficiency.
- *Third space loss*: Pancreatitis, intestinal obstruction, peritonitis
- Cerebral salt wasting syndrome

Hypervolemic hyponatremia
- Congestive heart failure
- Renal failure
- Cirrhosis

Pathophysiology of Hyponatremia

- Most causes of hyponatremia are associated with low serum osmolality. In general, hypotonic hyponatremia is due to either a primary water gain (and secondary Na^+ loss) or a primary Na^+ loss (and secondary water gain).
- Isotonic or slightly hypotonic hyponatremia may complicate transurethral resection of the prostate because large volumes of isoosmotic (mannitol) or hypoosmotic (sorbitol or glycine) bladder irrigation solution can be absorbed and result in a dilutional hyponatremia.
- Hypertonic hyponatremia is usually due to hyperglycemia or, occasionally, intravenous administration of mannitol. Glucose is an effective osmole and draws water from muscle cells, resulting in hyponatremia. Plasma Na^+ concentration falls by 1.4 mmol/L for every 100 mg/dl rise in the plasma glucose concentration.
- Diuretic-induced hyponatremia is almost always due to thiazide diuretics, because loop diuretics decrease the tonicity of the medullary interstitium and impairs maximal urinary concentrating capacity. This limits the ability of ADH to promote water retention.

Effects of Hyponatremia on Brain

- The fall in serum osmolality due to hyponatremia creates an osmolar gradient that favors water movement into the cells, leading to brain edema.
- Hyponatremia-induced cerebral edema occurs primarily with rapidly (over one to three days) developing hyponatremia. In slowly developing hyponatremia, there is time for adaptation of neuronal cells and hence, this can be clinically asymptomatic.

Clinical Manifestations

- Mild hyponatremia (plasma sodium level >120 mEq/L) is usually asymptomatic. Nausea and malaise are the earliest findings seen with mild hyponatremia.
- Headache, lethargy, obtundation, seizures, coma, and respiratory arrest may be seen at sodium level below 115 mEq/L.
- Chronic hyponatremia may be asymptomatic or associated with nonspecific features such as fatigue, nausea, dizziness, gait disturbances, forgetfulness, confusion, lethargy, and muscle cramps.

Investigations

- Serum sodium level is less than 135 mEq/L.
- Serum osmolality further characterizes hyponatremia into isotonic, hypertonic, and hypotonic hyponatremia.
- Urine sodium and urine osmolality is inappropriately increased in SIADH.
- Appropriate tests to rule out cardiac, renal, or liver disease.
- Thyroid function tests and cortisol levels.

Management

- Treatment of hyponatremia depends on the degree and rapidity of development of hyponatremia.
- Mild hyponatremia (Na >120) may not rapid development of hyponatremia (over hours to days) has high morbidity due to cerebral edema, and may be associated with altered sensorium or seizures. It is generally safe to correct this relatively rapidly using hypertonic saline infusions (1.6% or 3% saline).
- On the other hand, rapid correction of hyponatremia which has developed slowly (over weeks to months) can be hazardous to the brain. In these situations, an abrupt increase in extracellular osmolality can lead to neuronal dehydration and detachment from their myelin sheaths (central pontine myelinolysis—CPM)). CPM presents as quadriparesis, dysarthria, dysphagia and altered sensorium and is generally fatal. Hence, in chronic hyponatremia, correction should be slow and not exceed 10 mEq/L/day.
- Underlying cause of hyponatremia should be corrected always. For hypovolemic patients, this will require intravenous saline infusion. SIADH requires fluid restriction and treatment with demeclocycline to enhance water excretion, by interfering with collecting duct responsiveness to ADH. Conivaptan or tolvaptan which are ADH receptor antagonists are also useful in SIADH. Hypervolemic patients (due to CCF) are treated with a combination of diuretics and fluid restriction.

Q. Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

- In SIADH, increased (inappropriate) ADH release occurs without any physiologic stimulation. Hypovolemia and hyperosmolality are physiological stimulations for ADH secretion, so the diagnosis of SIADH is made only if these are absent. Inappropriate ADH secretion leads to water retention leading to hyponatremia.
- Normal regulation of ADH release occurs from both CNS and chest via baroreceptors and neural input. Hence, disorders affecting CNS and lungs commonly produce SIADH.

Causes

CNS disorders
- Head trauma, stroke, subarachnoid hemorrhage, brain tumor, encephalitis, meningitis

Lung diseases
- Tuberculosis, pneumonia, bronchiectasis, neoplasms

Malignancies
- Bronchogenic carcinoma, malignant lymphoma, leukemia

Drugs
- Carbamazepine, phenytoin, haloperidol, cyclophosphamide, chlorpropamide

Others
- Postoperative state, sustained pain, stress, nausea, AIDS, idiopathic

Clinical Features of SIADH

- These are same as those given under hyponatremia. Clinical features of underlying disease may also be present.

Diagnosis of SIADH

- Hyponatremia
- Low plasma osmolality <270 mmol/kg.
- Urine osmolality >150 mmol/kg. Normally urine should be maximally dilute in the presence of low serum osmolality, but is typically >150 in SIADH, i.e. inappropriately concentrated due to ADH action.
- Urine sodium concentration >30 mmol/l.
- Normal renal function tests, uric acid.
- Exclusion of other causes of hyponatremia.
- Appropriate clinical context.

Treatment

- Severe symptomatic hyponatremia should be corrected using hypertonic saline.
- Fluid restriction to 600–1000 ml/day.
- Treatment of the cause of SIADH (e.g. withdrawal of a drug causing SIADH).
- Demeclocycline (600–900 mg/day) may enhance water excretion, by interfering with collecting duct responsiveness to ADH.
- Oral urea therapy (30–45 g/day) can provide a solute load to promote water excretion.
- ADH receptor antagonists are the new drugs available to treat SIADH. These are conivaptan and tolvaptan. They promote the excretion of free water (aquaretics).

Q. Hypernatremia.

- Serum sodium level of >145 mEq/L is called hypernatremia.

- Hypernatremia is either due to excess water loss from the body or due to excess sodium intake. Most of the cases are due to excess free water loss from the body.
- An intact thirst mechanism usually prevents hypernatremia. Hence, whatever may be the underlying cause, hypernatremia occurs only if adequate water intake is not possible, as with unconscious patients.

Causes

- Excessive diuretic therapy due to relatively more water loss than sodium loss.
- Primary water loss due to diarrhea or excessive sweating.
- Diabetes insipidus (central or nephrogenic).
- Excess sodium intake (IV or oral salt administration).

Clinical Features

- Hyperthermia, delirium, and coma may be seen with severe hypernatremia.

Treatment

- Correction of underlying cause.
- Fluids without sodium, such as 5% dextrose should be administered to correct hypernatremia. Fluids should be administered over a 48-hour period, aiming for a decrease in serum sodium of 1 mEq/L/h.

Q. Discuss briefly about the normal handling of potassium by the body.

- Potassium is abundant in meat, fruits (especially bananas), and coconut water. The usual dietary intake of potassium is between 80 and 160 mEq per day. Serum concentration is between 3.5 to 5 mEq/L.
- Most of the body's potassium is intracellular. Hence, massive destruction of cells (e.g. hemolysis, rhabdomyolysis) can release large amount of potassium into the circulation.
- An excess potassium load is handled by: Uptake into cells, renal excretion and extrarenal losses (e.g. gastrointestinal).
- Uptake of potassium into cells is governed by the activity of the Na^+/K^+-ATPase in the cell membrane and by H^+ concentration. Uptake is stimulated by: Insulin, beta-adrenergic stimulation and alkalosis. Uptake is decreased by: Alpha adrenergic stimulation and acidosis (K^+ exchanged for H^+ across cell membrane).
- Kidneys are responsible for the excretion of 90% of the potassium taken in diet. Renal excretion of potassium is increased by aldosterone, which stimulates K^+ and H^+ secretion in exchange for Na^+ in the collecting duct. Because H^+ and K^+ are interchangeable in the exchange mechanism, acidosis decreases and alkalosis increases the secretion of K^+. Aldosterone secretion is stimulated by hyperkalemia and inhibited by hypokalemia. Many drugs affect K^+ homeostasis by affecting aldosterone release (e.g. heparin, NSAID, ACE inhibitors) or by directly affecting renal potassium handling (e.g. diuretics). In the presence of decreased potassium intake, reduction of renal excretion of potassium may take 1–2 weeks. During this time hypokalemia may develop.
- About 10% of daily potassium intake is excreted in the gastrointestinal tract. Excessive vomiting, diarrhea, and colorectal villous adenomas can lead to hypokalemia.

Q. Enumerate the causes of hypokalemia. Discuss briefly the clinical features, ECG manifestations and management of hypokalemia.

- Hypokalemia is defined as plasma K^+ concentration of <3.5 mEq/L.

Etiology

Reduced intake
- Diet containing less K^+, starvation, potassium free IV fluids.

Urinary loss
- Diuretics, polyuria, primary mineralocorticoid excess, metabolic acidosis, hypomagnesemia, amphotericin-B, salt-wasting nephropathies including Bartter's or Gitelman's syndrome.

Gastrointestinal loss
- Vomiting, diarrhea, tube aspiration of gastric contents, laxative abuse, villous adenoma.

Increased entry into cells
- Alkalosis, increased availability of insulin, β_2 agonists, hypokalemic periodic paralysis.

Clinical Features

- Muscular weakness and paralysis. Respiratory muscle weakness can lead to respiratory failure and death. Gastrointestinal muscle weakness leads to paralytic ileus.
- Cardiac arrhythmias include ectopic beats, sinus bradycardia, paroxysmal atrial or junctional tachycardia, atrioventricular block, and ventricular tachycardia or fibrillation.
- Muscle cramps leading to rhabdomyolysis and myoglobinuria.

Investigations

- Serum electrolytes, bicarbonate, calcium and magnesium.
- Urine potassium excretion is increased in hypokalemia due to renal loss and decreased in extrarenal loss.
- Plasma renin activity and aldosterone levels will identify patients with primary hyperaldosteronism.

- ECG changes—depression of ST segment, flattening or inversion of T wave, and presence of U waves at the end of the T wave. U waves are often seen in leads V4 to V6.

Management

- Treatment of the underlying cause.
- Potassium replacement—this can be done by oral (as syrup) or IV potassium chloride supplementation. For mild hypokalemia (K^+ >3 mEq/L), about 20 to 80 mEq per day of oral potassium chloride is given in 3 to 4 divided doses. In moderate hypokalemia (K^+ <3.0 mEq/L), about 120 mEq oral potassium chloride is given in 3 to 4 divided doses. For severe or symptomatic hypokalemia, intravenous potassium chloride is given. IV potassium is administered along with IV fluids at a concentration of 20 to 40 mEq per liter of fluid.
- Potassium sparing diuretics—such as spironolactone or amiloride can be used along with other measures to correct hypokalemia.

Q. Enumerate the causes of hyperkalemia. Discuss briefly the clinical features, ECG manifestations and management of hyperkalemia.

- Hyperkalemia is defined as a plasma K^+ concentration of >5.5 mEq/L.

Causes

Excess intake
- K^+ rich foods, intravenous fluid containing K^+.

Impaired excretion
- Acute and chronic renal failure, Addison's disease, hypoaldosteronism, drugs (K^+ sparing diuretics, ACE inhibitors, NSAIDs).

Release of intracellular K^+
- Hemolysis, rhabdomyolysis, crush injury, burns, tumor lysis syndrome.

Shift of K^+ out of cell
- Metabolic acidosis, hyperosmolality, insulin deficiency, hyperkalemic periodic paralysis, succinylcholine, digitalis.

Pseudohyperkalemia
- Hemolysed blood sample, repeated fist clenching during phlebotomy, with release of K^+ from forearm muscles, specimen drawn from arm with K^+ infusion.

Clinical Features

- Symptoms generally do not occur until the plasma potassium concentration exceeds 7 mEq/L, unless the rise in potassium concentration has been very rapid.
- Hyperkalemia interferes with normal neuromuscular function and causes muscle weakness, and rarely, flaccid paralysis. This happens repeatedly in hyperkalemic periodic paralysis.
- Paralytic ileus and abdominal distension may occur.
- Hyperkalemia causes depolarization, leading to decreased cardiac excitability, hypotension, and bradycardia. Ventricular fibrillation and cardiac arrest are terminal events.
- *ECG changes*: Tall peaked T waves with shortened QT interval are the first changes seen on the ECG. This is followed by progressive lengthening of the PR interval and QRS duration. The P wave may disappear, and QRS widens giving rise to "sine wave" pattern. A variety of other conduction disturbances, including right bundle branch block, left bundle branch block, bifascicular block, and advanced atrioventricular block may also be seen

Treatment

- Discontinue exogenous K^+ intake by eliminating K^+ rich foods such as fruits, coconut water, etc.
- Calcium gluconate decreases membrane excitability and prevents cardiac arrhythmias. The usual dose is 10 ml of a 10% solution intravenously over 2–3 mins.
- Insulin plus dextrose infusion shifts K^+ into the cells and temporarily lowers the plasma K^+ concentration. 50 ml of 50% dextrose plus 10 units of regular insulin is given every 6 to 8th hourly.
- Sodium bicarbonate increases blood pH and results in a shift of K^+ into cells. 1–2 ampoules can be given intravenously.
- β_2-adrenergic agonists such as salbutamol promote cellular uptake of K^+. They can be given parenterally or in nebulized form every 4 to 6th hourly.
- K^+ excretion can be enhanced by diuretics (frusemide, thiazides) and cation-exchange resin. Sodium polystyrene sulfonate (e.g. K-BIND) is a cation-exchange resin that binds to K^+ in the gastrointestinal tract which is then excreted in the stools.
- Hemodialysis is the most rapid way of removing the K^+ from the body. It is indicated in patients with renal failure and those with severe hyperkalemia unresponsive to other measures. Peritoneal dialysis also removes K^+ but is less effective.
- Underlying cause of hyperkalemia should be identified and corrected.

Q. Hypomagnesemia.

- Normal magnesium level in the plasma is 1.4 to 2 mg/dl. A value less than this is called hypomagnesemia.

Causes

Decreased intake or absorption
- Malnutrition, alcoholism, malabsorption, chronic diarrhea, laxative abuse, gastrointestinal suction, total parenteral nutrition

Increased renal loss
- Diuretics, hyperaldosteronism, hyperparathyroidism, hyperthyroidism, hypercalcemia, tubulointerstitial diseases

Others
- Diabetes mellitus, post parathyroidectomy (hungry bone syndrome), respiratory alkalosis, pregnancy

Clinical Features

- Anorexia, nausea, vomiting, lethargy, weakness, and personality change.
- Tetany (e.g. positive Trousseau's or Chvostek's sign or spontaneous carpopedal spasm, hyperreflexia), and tremor and muscle fasciculations.
- Severe hypomagnesemia may cause generalized tonic-clonic seizures, especially in children.

Investigations

- Urinary excretion of magnesium—more than 10–30 mg/d indicates renal magnesium loss.
- Hypocalcemia and hypokalemia may be present.
- ECG shows prolonged QT interval.

Treatment

- In mild, asymptomatic cases, oral magnesium gluconate (500 to 1000 mg two to three times daily is given for 3 to 4 days.
- In symptomatic cases, IV infusion of 1–2 g of magnesium sulfate, followed by an infusion of 6 g magnesium sulfate in at least 1 L of fluids over 24 hours, repeated for up to 7 days to replete magnesium stores. Magnesium sulfate may also be given intramuscularly.

Q. Hypermagnesemia.

- Hypermagnesemia is a serum Mg concentration >2.1 mEq/L.
- It occurs most commonly in patients with renal failure after ingestion of Mg-containing drugs, such as antacids or purgatives. Other causes are administration of magnesium sulfate intravenously (as a treatment for eclampsia and aluminium phosphide poisoning).
- Symptoms and signs include hyporeflexia, hypotension, respiratory depression, and cardiac arrest.
- Treatment of severe Mg toxicity consists of intravenous Ca gluconate. IV furosemide can increase Mg excretion when renal function is adequate. Hemodialysis may be considered in severe hypermagnesemia.

Q. Discuss the normal physiology of acid–base balance.

Or

Q. Discuss how the body maintains normal pH.

- The concentration of hydrogen ions in both extracellular and intracellular compartments is tightly controlled. The pH of ECF including blood is maintained between 7.36–7.44 (average 7.40). Maintenance of pH within this range is important, otherwise, all the metabolic functions of the body get affected leading ultimately to death.
- A decrease in extracellular fluid pH is called acidosis which is equivalent to raising the hydrogen concentration. An increase in extracellular fluid pH is called alkalosis which is equivalent to lowering the hydrogen concentration.
- Acidosis is two types; metabolic acidosis and respiratory acidosis. Metabolic acidosis is associated with a low pH and low bicarbonate concentration. Respiratory acidosis is associated with a low pH and high pCO_2.
- Alkalosis is also of two types; metabolic alkalosis and respiratory alkalosis. Metabolic alkalosis is associated with a high pH and high bicarbonate concentration. Respiratory alkalosis is associated with a high pH and low pCO_2.
- Body maintains the pH within normal limits by a variety of physiological mechanisms.

Maintenance of Normal pH by the Body

- There are many buffer systems in the body which prevent wide swings in the pH of the ECF.

Carbonic Acid/Bicarbonate Buffer System

- Most important because it immediately corrects the swing in pH. Any acid load in the form of H^+ ions combine with bicarbonate to form carbonic acid, which, then dissociates to form CO_2 and water. CO_2 thus produced is excreted by the lungs.
- This system is a major buffer in the plasma, within the cells including RBCs and bone.
- Hemoglobin is the most important buffer within RBCs and can buffer large amount of H^+ ions.
- Bone contains large amount of bicarbonate which can buffer acid load.

Pulmonary Mechanisms

- Respiratory compensation for acid–base disturbances can occur quickly, due to alterations in ventilatory drive mediated through pH changes in the brainstem.
- In acid accumulation, ventilation is increased, thus washing out CO_2 which is equivalent to carbonic acid

thus increasing the pH. Conversely, alkalosis leads to inhibition of ventilation and accumulation of CO_2 leading to decrease in pH.

Renal Mechanisms

- Kidneys provide third line of defense against acid–base disturbances. When acid accumulates, kidneys increase urinary excretion of acid, and conserve bicarbonate.

Q. Discuss the causes, clinical features, investigations and management of metabolic acidosis.

- Metabolic acidosis is be defined as a disorder associated with a low pH and low bicarbonate concentration.
- It can be produced by three major mechanisms:
  - Increased acid production (e.g. ketoacidosis and lactic acidosis).
  - Loss of bicarbonate (e.g. diarrhea or type 2 renal tubular acidosis).
  - Decreased renal acid excretion (e.g. renal failure or type 1 renal tubular acidosis).
- The pH fall is compensated by hyperventilation, resulting in a reduced pCO_2. Kidneys try to compensate by increasing the excretion of acid load and conserving bicarbonate. Respiratory compensation is immediate, but renal compensation takes many days.
- Based on the nature of accumulating acid, two types of metabolic acidosis can be defined; normal anion gap acidosis and high anion gap acidosis.
- In normal anion gap acidosis, a mineral acid (HCl) accumulates, or there is a primary loss of bicarbonate buffer from the ECF. Here, there is no addition of new acidic anion to the plasma. Hence, the anion gap $(Na^+ + K^+) - (Cl^- + HCO_3^-)$, remains normal (15 mmol/L) since the plasma chloride increases to replace the depleted bicarbonate levels. Normal anion gap is due to anions such as phosphate, sulphate and multiple negative charges on plasma protein molecules. Examples of normal anion gap metabolic acidosis are diarrhea and type 2 renal tubular acidosis.
- In high anion gap acidosis, an accumulating acid is accompanied by its corresponding anion, which adds to the unmeasured anion gap, while the chloride concentration remains normal. Examples are ketoacidosis and lactic acidosis.

Causes

Increased acid production
- Lactic acidosis
- Ketoacidosis (diabetes, starvation, alcohol-associated)
- Ingestions (methanol, ethylene glycol, aspirin)

Loss of bicarbonate
- Diarrhea
- Ureterosigmoidostomy
- Proximal renal tubular acidosis

Decreased renal acid excretion
- Renal failure, distal renal tubular acidosis

Clinical Features

- Kussmaul breathing—deep sighing respiration.
- Abdominal pain and vomiting.
- Neurologic abnormalities—irritability, lethargy, seizures and coma.

Investigations

- Arterial blood gas analysis—pH, pCO_2, and the bicarbonate concentration can be known by this. Low serum bicarbonate and low pH confirms the diagnosis of metabolic acidosis. pCO_2 is decreased due to respiratory compensation.
- Renal function tests.
- LFT.
- Serum electrolytes such as sodium and potassium.
- Blood sugar (to rule out diabetic ketoacidosis).
- Lactic acid levels if indicated.

Management

- Identify and correct the underlying cause.
- Use of sodium bicarbonate infusion is indicated when the underlying disorder cannot be readily corrected or when the acidosis is severe (pH <7).
- Sodium bicarbonate and potassium supplements are needed to achieve normal plasma bicarbonate and potassium levels in proximal and distal renal tubular acidosis.

Q. Anion gap.

- The anion gap is the difference in the measured cations (positively charged ions) and the measured anions (negatively charged ions) in serum, plasma, or urine.
- It is calculated by subtracting the serum concentrations of chloride and bicarbonate (anions) from the concentrations of sodium and potassium (cations):

$$\text{Anion gap} = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

- Normal value for the serum anion gap is 8–16 mEq/L. Anion gap can be high, normal or low.
- Anion gap is useful in knowing the cause of metabolic acidosis, because the causes of high and normal anion gap acidosis are different.

Causes of High Anion Gap Acidosis

- Lactic acidosis, diabetic ketoacidosis, methanol and ethylene glycol ingestion, uremia.

Causes of Normal Anion Gap Acidosis

- Diarrhea, renal tubular acidosis.

Q. Metabolic alkalosis.

- Metabolic alkalosis is characterized by an increase plasma pH and bicarbonate concentration. There is a compensatory rise in pCO_2 due to hypoventilation.

Causes

- GI loss of hydrogen ion, e.g. vomiting or aspiration of gastric contents.
- Renal loss of hydrogen, e.g. primary and secondary hyperaldosteronism, diuretic use, Bartter's syndrome, Gitelman syndrome.
- Intracellular shift of hydrogen—due to hypokalemia.
- Alkali administration.

Clinical Features

- Tetany (carpopedal spasm) due to increased neuromuscular irritability as the plasma ionized calcium falls.
- Alkalosis also lowers threshold for anginal symptoms and arrhythmias.
- Manifestations of underlying cause.

Management

- Treat the underlying cause.
- Replacement of potassium in hypokalemia induced alkalosis.

Q. Respiratory acidosis.

- Respiratory acidosis occurs when there is accumulation of CO_2 due to reduced alveolar ventilation. Renal retention of bicarbonate partially compensates for acidosis; hence, there is rise in plasma bicarbonate concentration.
- Respiratory acidosis can be acute or chronic.

Causes

- *Conditions that impair CNS respiratory drive*: Encephalitis, brainstem disease, drugs (opioids, benzodiazepines, barbiturates).
- *Respiratory muscle weakness*: e.g. myesthenia gravis, Guillain-Barré syndrome, muscular dystrophy, cervical cord lesions.
- *Lung diseases*: COPD, acute exacerbation of asthma, interstitial lung disease, pneumothorax.
- *Chest wall disorders*: Severe kyphoscoliosis, flail chest.
- Obesity-hypoventilation syndrome, obstructive sleep apnea (OSA).

Clinical Features

- Features of underlying disease.
- Bounding pulse, drowsiness or coma due to CO_2 accumulation.

Management

- Correct the underlying cause.
- Ventilatory support if required.
- $NaHCO_3$ is almost always contraindicated, because HCO_3^- can be converted to pCO_2 in serum.

Q. Respiratory alkalosis.

- Respiratory alkalosis develops when there is reduction of pCO_2 due to hyperventilation resulting in increase in plasma pH. If hyperventilation is prolonged, renal compensation occurs so that acid secretion is reduced and bicarbonate excretion is increased.
- Causes of hyperventilation include anxiety states, overvigorous assisted ventilation, pregnancy, pulmonary embolism, chronic liver disease, and salicylate poisoning.
- Clinical features include those of underlying cause. Reduction in ionized calcium due to alkalosis produces agitation, perioral and digital tingling, carpopedal spasm, Trousseau's sign and Chvostek's sign. Seizures may develop in severe cases.
- Management involves correction of the underlying cause. In acute hyperventilation due to anxiety, rebreathing into a paper bag will increase the pCO_2. Sedation may be needed if anxiety and hyperventilation persists.

Oncology

14

Q. What is cancer? Discuss briefly about the etiology of cancer.

- Cancer refers to unregulated cell growth with tissue invasion/metastasis. Unregulated cell growth without invasion is called benign neoplasms, or new growths. Cancer is a synonym for *malignant neoplasm*.
- Cancers of epithelial tissues are called *carcinomas*; cancers of nonepithelial (mesenchymal) tissues are called *sarcomas*. Cancers arising from hematopoietic or lymphoid cells are called *leukemias* or *lymphomas*.

Etiology

- The cause of most cancers remains unknown. However, the following factors have been identified to cause cancer.

Genetic Factors

- This is the most important cause of cancer development.
- Most tumors exhibit chromosomal abnormalities such as deletions, inversions, translocations, or duplications. This leads to activation of proto-oncogenes to oncogenes or deletion of tumor suppressor genes or both. Both these changes cause abnormal cellular proliferation and cancer formation.

Viruses

- The role of viruses in carcinogenesis is well-known. Epstein-Barr virus (EBV) is associated with Burkitt's lymphoma and nasopharyngeal cancer. Hepatitis B and C virus can lead to hepatocellular carcinoma. *Helicobacter pylori* infection is associated with non-Hodgkin's lymphoma and stomach Ca. Human T-lymphotropic virus type I (HTLV-I) is associated with adult acute T cell leukemia. Kaposi's sarcoma is seen in HIV infection. Human papillomaviruses (HPV) can cause cervical cancer in women.

Aging

- Age is most significant factor for cancer development. Two-thirds of all cancers occur above the age of 65 years. This is due to alteration of host cells, longer exposure to carcinogens, and decreased immunity.

Ionizing Radiation

- Natural sources (cosmic rays, soil) or man-made ionizing radiation (diagnostic, therapeutic, atomic bomb explosion) can lead to skin cancer and leukemia.

Ultraviolet (UV) Radiation

- UV rays from the sun, particularly (UV-B spectrum 240–230 nm) can cause skin cancer or melanoma.

Tobacco

- Smoking and chewing tobacco has been identified as a major cause of lung and oral cancer. Cancers of esophagus, stomach, bladder, kidney, liver and larynx are also related to tobacco carcinogens which are primarily polycyclic hydrocarbons and cyclic N-nitrosamine.

Occupational Hazards

- Chimney sweepers had a high incidence of scrotal cancer which was attributed to soot. Bladder cancer has been noted in aniline dye workers. Asbestos exposure is associated with mesothelioma and lung cancer.

Environmental Pollution

- Air pollution caused by industries and exhaust from vehicles contains polycyclic hydrocarbons; these hydrocarbons cause lung cancer.

Drugs and Toxins

- Cancer chemotherapeutic drugs can cause leukemia. Aflatoxin increases the chance of hepatocellular Ca.

Diet and Alcohol

- Meat and fat increase the risk of colon cancer. Salt intake and salted fish in diet increase the risk of stomach cancer and nasopharyngeal cancer, respectively.

Q. Discuss briefly about the genetic factors in the causation of cancer.

Q. Genetic basis of transformation of a normal cell into a malignant cell.

Q. Proto-oncogene, oncogene and tumor suppression genes.

- Most tumors exhibit genetic abnormalities such as deletions, inversions, translocations, or duplications.
- Most genetic abnormalities lead to activation of proto-oncogenes to oncogenes or deletion of tumor suppressor genes or both. Both these changes cause abnormal cellular proliferation and cancer formation.

Proto-oncogenes and Oncogenes

- Oncogenes were initially discovered in the genome of retroviruses capable of causing cancers in chickens, mice, and rats. Proto-oncogenes in the normal state stimulate the normal growth of cells. Activated proto-oncogenes are called oncogenes and are responsible for the development of cancers. Activation of proto-oncogenes to oncogenes can occur due to point mutation, DNA amplification, chromosomal rearrangement and viral infections.
- *Point mutation* is a common mechanism of oncogene activation. Point mutations occur due to ionizing radiation, ultraviolet rays, and carcinogens.
- *DNA amplification*—DNA sequence amplification is another mechanism of proto-oncogene activation and leads to overexpression of the gene product. Numerous genes have been reported to be amplified in cancer. Because the region amplified often extends to hundreds of thousands of base pairs, more than one oncogene may be amplified in some cancers. Demonstration of amplification of a cellular gene is often a predictor of poor prognosis. For example, *ERBB2/HER2* and *NMYC* are often amplified in aggressive breast cancers and neuroblastoma, respectively.
- *Chromosomal rearrangement* in Burkitt's lymphoma, the *c-myc* oncogene is activated by translocation of genetic material from chromosome 8 to chromosome 14. CML is caused by reciprocal translocation of the long arms of chromosomes 9 and 22, resulting in the generation of a fusion protein (BCR-ABL) with tyrosine kinase activity. Amplification of the HER-2/neu oncogene in breast cancer has been associated with more aggressive tumors.
- *Viruses*—viral DNA may integrate within a proto-oncogene and may activate it. Viral DNA may also contain proto-oncogene which may be transferred to the host after infection. Viruses may also activate growth-promoting pathways and inhibit tumor-suppressor products in the infected cells.

Tumor Suppressor Genes

- The *p53* gene triggers programmed cell death (apoptosis). Mutations in the *p53* gene lead to abnormal cell proliferation and cancer formation. *RB* gene is a tumor suppressor gene, and its inactivation leads to development of retinoblastoma. Many soft tissue sarcomas are produced due to inactivation of tumor suppressor genes.

Q. Cancer screening.

- Early detection of cancer offers a chance of cure. When patients are diagnosed with a cancer on the basis of symptoms, the cancer may have already spread in a significant proportion, so that curative treatment (usually surgical) is not possible. Early detection of cancer in an asymptomatic population can identify people with cancer which may be curable.

Requirements of a Screening Programme

- Acceptable to the population.
- Capable of detecting high percentage of early cancers.
- Low false-positive rate (reducing unnecessary interventions).
- Cost effective.
- Availability of an effective intervention.

Table 14.1 Cancers with potential for screening

Malignancy	Method of screening	Population to be screened
• Breast cancer	Mammography, breast self-examination	Females 40 and above, every year
• Cervical cancer	Cervical smear cytology (Pap smear)	*Females*: 18–65, every 1–3 years
• Prostate cancer	Serum prostate-specific antigen (PSA) level	Males of 50 years of age and above, every year
• Colorectal cancer	Single flexible sigmoidoscopy, fecal occult blood test	50 years of age and above, every 5 to 10 years

Q. Tumor markers.

- A tumor marker is a biomarker found in the blood, urine, or body tissues that can be elevated in cancer. Most of the tumor markers are proteins secreted by the tumor into the circulation.

Examples: Tumor Markers

- *Carcinoembryonic antigen (CEA)*: Cancers of gastro-intestinal tract, lung, breast.
- *CA-19*: Colon and pancreas.
- *CA-125*: Ovary.
- *Alpha-fetoprotein (AFP)*: Hepatocellular carcinoma and malignant teratoma
- *Lactate dehydrogenase (LDH)*: Most cancers, reflecting tumor burden or necrosis
- *Prostate-specific antigen (PSA)*: Prostate cancer
- *β_2-microglobulin*: Elevated in multiple myeloma.
- *Human chorionic gonadotropin (HCG)*: Germ cell tumors of testes and ovaries, choriocarcinoma.
- *Calcitonin*: Medullary carcinoma thyroid.
- *Thyroglobulin*: Postoperative marker for thyroid cancer (but not for medullary cancer).
- *Chromogranin-A*: Neuroendocrine tumor.

Uses of Tumor Markers

- To detect the presence of cancer.
- Levels may reflect the extent (stage) of the cancer.
- To follow response to therapy.
- To screen for recurrence of cancer.

Q. Enumerate oncologic emergencies.

Due to local effect
- Spinal cord compression, superior vena cava syndrome, malignant effusions

Systemic effects
- Tumor lysis syndrome, hypercalcemia, opportunistic infections, hyperuricemia, SIADH

Hematologic
- Hypercoagulability, thrombocytopenia, febrile neutropenia, DIC

Q. Tumor lysis syndrome.

- Tumor lysis syndrome refers to a group of metabolic complications due to sudden destruction of tumor cells. It usually occurs after the treatment of neoplastic disorders.
- It is commonly seen in lymphomas, leukemias and multiple myeloma.

Pathophysiology

- Lysis of large number of tumor cells releases intracellular potassium and phosphate causing hyperkalemia and hyperphosphatemia. Sudden destruction of tumor cells also leads to hyperuricemia. Uric acid crystals may get deposited in renal tubules leading to renal failure.
- Hypocalcemia is a consequence of acute hyperphosphatemia with subsequent precipitation of calcium phosphate in soft tissues.
- Acute renal failure and the liberation of large amounts of endogenous intracellular acids from cellular catabolism result in metabolic acidosis.

Clinical Features

- Dysuria, oliguria, hematuria may be present due to uric deposition in kidneys and consequent AKI. Uremia due to AKI may produce fatigue, weakness, nausea, vomiting and anorexia.
- Hyperkalemia may produce muscle weakness and cardiac arrhythmias.
- Hypocalcemia may produce tetany, and seizures.

Investigations

- Serum uric acid, phosphate and potassium are elevated. Serum calcium decreased (hypocalcemia).
- Urea and creatinine are elevated due to renal failure.
- ABG shows metabolic acidosis.
- ECG.
- Other routine investigations.

Treatment

- *Hydration*: Volume depletion is a major risk factor for tumor lysis syndrome and must be corrected vigorously. Intravenous fluids along with loop diuretics are given to maintain high urine output so that uric acid crystals are easily washed out in the urine thus preventing uric acid nephropathy.
- Hyperuricemia is treated with *allopurinol and rasburicase*. Allopurinol blocks conversion of hypoxanthine and xanthine to uric acid. Rasburicase is a recombinant urate oxidase which converts uric acid into an inactive and soluble metabolite (allantoin) which is easily excreted by the kidneys. *Febuxostat* is a new xanthine oxidase inhibitor which is long acting and does not require dose modification in renal failure. Febuxostat can be used instead of allopurinol.
- Hyperkalemia is treated with antihyperkalemia measures such as β_2 agonists, insulin plus dextrose infusions and potassium binding resins.
- Hypocalcemia is treated with intravenous infusion of calcium gluconate.

- Hyperphosphatemia is managed with oral phosphate binders and the same solution insulin plus dextrose solution used for the control of hyperkalemia.
- Urinary alkalinization will convert uric acid to more soluble urate salt, thus preventing deposition of uric acid crystals in the renal tubules and consequent renal failure. Sodium bicarbonate is given intravenously for this purpose.
- Hemodialysis should be considered in severe cases.

Q. Spinal cord compression due to tumor.

- Tumor can directly compress the spinal cord or damage it indirectly by interfering with blood supply.

Clinical Features

- Back pain at the level of the spinal cord lesion.
- Progressive weakness and sensory loss below the level of compression.
- Radiculopathy due to nerve root compression.
- Bowel and bladder dysfunction.

Investigations

- Plain X-rays may show bony destruction.
- MRI is essential to demonstrate tumor detail and spinal cord compression.
- Biopsy of the lesion may be required to confirm the diagnosis of malignancy.

Treatment

- Immediate diagnosis and treatment is essential to prevent permanent neurological deficits.
- Inj dexamethasone 100 mg is given IV stat followed by 25 mg IV 6-hourly.
- Urgent radiotherapy.
- Surgery is indicated if neurologic deficits worsen despite nonsurgical treatment, a biopsy is needed, spine is unstable or tumor recurs after radiation therapy.

Q. Paraneoplastic syndromes.

- Paraneoplastic syndromes are disorders due to the remote effects of malignancy that cannot be attributed either to direct invasion or metastatic lesions.
- They may affect up to 15% of patients with cancer. The most common cancer associated with paraneoplastic syndromes is small cell cancer of the lung.
- These syndromes may be the first sign of a malignancy and provide an early clue to the presence of certain types of cancer. Treatment of the cancer leads to resolution of the syndrome, and, conversely, recurrence of the cancer may be heralded by the return of the syndromes.

Mechanism of Paraneoplastic Syndromes

- Paraneoplastic syndromes result from the production and release of physiologically active substances by the tumor. Tumors may produce hormones, hormone precursors, a variety of enzymes, or cytokines. Paraneoplastic syndromes associated with ectopic hormone production are the best characterized entities. Examples are hypercalcemia due to production of parathyroid hormone (PTH) or PTH-related peptide by squamous cell Ca of lung and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) due to ADH secretion by small cell Ca.
- Antibodies produced against tumor cells may cross react and destroy normal tissues producing paraneoplastic manifestations. Many neurologic paraneoplastic syndromes have been found to be caused by the production of antineuronal antibodies.
- In some cases the pathophysiology of paraneoplastic syndromes is unknown.

Manifestations of Paraneoplastic Syndromes

Systemic
- Anorexia
- Cachexia
- Weight loss
- Fever
- Suppressed immunity

Endocrine
- Cushing's syndrome
- SIADH
- Hypercalcemia
- Hypoglycemia
- Carcinoid syndrome

Neuromuscular
- Peripheral neuropathy (most common neurologic paraneoplastic syndrome)
- Subacute cerebellar degeneration
- Eaton-Lambert syndrome
- Stiff man syndrome

Hematologic
- Erythrocytosis
- Pure red cell aplasia
- Eosinophilia
- Thrombocytosis
- Coagulopathy

Rheumatologic
- Arthropathies
- Hypertrophic osteoarthropathy
- Dermatomyositis/polymyositis

Cutaneous
- Itching
- Dermatomyositis
- Acanthosis nigricans
- Sweet's syndrome

Others
- Amyloidosis
- Hypertrophic pulmonary osteoarthropathy

Management

- Treatment of underlying cancer leads to resolution of paraneoplastic syndromes. Life-threatening paraneoplastic emergencies such as hypercalcemia should be treated appropriately.
- Immunosuppression (steroids), intravenous immunoglobulins, or plasma exchange can be used in patients with autoantibodies causing paraneoplastic manifestations.

Q. Targeted therapy in the treatment of cancer.

- Conventional cancer therapy (radiotherapy and chemotherapy) does not adequately discriminate between rapidly dividing normal cells and cancer cells. Hence, normal dividing cells also get killed leading to many side effects such as bone marrow suppression, alopecia, mucositis, etc.
- Targeted therapy uses specific molecular targets present exclusively on cancer cells (and not on normal cells) thus avoiding the side effects of conventional chemotherapy. These targets may be receptors or enzymes in the tumor cells. To be effective, molecular targets should have a role in cancer cell division and growth.
- Targeted therapy is often used with chemotherapy and radiotherapy for additive or synergistic effect.

Examples of Targeted Therapies

- Hormone therapies
- Signal transduction inhibitors
- Gene expression modulators
- Apoptosis inducers
- Angiogenesis inhibitors
- Immunotherapies.

Hormone Therapies

- Hormone therapies block a certain hormone required by the tumor to grow. Hormone therapies are used in the treatment of breast and prostate cancer.

Signal Transduction Inhibitors

- Block the activities of molecules that stimulate cell division.
- Examples are imatinib, a tyrosine kinase inhibitor used in the treatment of CML. Gefitinib and erlotinib inhibit tyrosine kinase in the epidermal growth factor receptors (EGFR). They have been tried in advanced non-small cell lung cancer.

Gene Expression Modulators

- Oncogene expression can be inhibited by triplex forming oligonucleotides, as well as peptide nucleic acids. Research is going on this.

Apoptosis Inducers

- They induce the cancer cells to undergo apoptosis (spontaneous cell death). Examples include *proteasome inhibitors*, such as bortezomib and carfilzomib. Proteosome-ubiquitin pathway is an essential intracellular system that degrades many labile proteins regulating cell cycle, apoptosis, and transcription. These drugs are used in refractory multiple myeloma.

Angiogenesis Inhibitors

- They block the growth of blood vessels supplying the tumor. Lack of blood supply interferes with tumor growth. Many of these drugs work by blocking *vascular endothelial growth factor* (VEGF) proteins or the VEGF receptors.
- Examples of angiogenesis inhibitors include bevacizumab and ramucirumab.

Immunotherapies

- They trigger the immune system to destroy cancer cells.
- Examples are monoclonal antibodies that recognize specific molecules on the surface of cancer cells. Binding of the monoclonal antibody to the target molecule results in the immune destruction of cells that express that target molecule. *Rituximab* is a monoclonal antibody against the B-lymphocyte antigen CD20. It is used in the treatment of resistant or relapsed lymphomas.
- Trastuzumab is a recombinant monoclonal antibody directed against the HER-2/*neu* gene product (a cells surface receptor) and is effective in the treatment of HER-2/*neu* expressing breast cancer.
- Monoclonal antibodies can also be used to deliver toxic molecules to cancer cells specifically (immunotoxin therapy). Once the antibody has bound to its target cell, the toxic molecule that is linked to the antibody, such as a radioactive substance or a toxin is taken up by the cell, ultimately killing that cell. Immunotoxin therapy is used in Hodgkin's lymphoma since the Reed-Sternberg cells express a large number of antigens that occur in only a small fraction of normal cells.

Q. Enumerate the various modes of treatment of cancer.

- Various modes of cancer treatment are as follows.

Surgery

- Surgery has a pivotal role in the management of cancer.
- It can be either curative or palliative. Surgery can be curative for most solid tumors if detected early. Palliative surgeries relieve the symptoms without curing the cancer.

Examples of palliative surgeries are debulking the tumor to relieve pressure symptoms, colostomy in colon cancer, and fixation of pathological fractures.

Chemotherapy

- Chemotherapy makes use of various cytotoxic drugs with different modes of action. Examples are melphalan, methotrexate, cyclophosphamide, etc.

Radiotherapy

- Radiotherapy makes use of ionizing radiation for the treatment of cancer.

Hormonal Treatments

- Makes use of hormones/hormone modifiers for the treatment of cancer.
- *Examples*: Reducing estrogen levels can reduce the proliferation of breast cancer cells and increase their loss through apoptosis. Anti-androgen therapy can help in prostate cancer.

Biological Treatments

- Rituximab is a monoclonal antibody against the B cell antigen CD20. It increases response rates and survival in non-Hodgkin's lymphoma.
- Trastuzumab is another monoclonal antibody which improves survival in patients with advanced breast cancer.

Targeted Therapies

- These therapies target a particular pathway in cancer cells with minimal or no effect on normal cells. This creates the potential to target cancer cells more selectively, with reduced toxicity to normal tissues.
- Example is imatinib which inhibits the *BCR-ABL* gene product tyrosine kinase that is responsible for chronic myeloid leukemia.

Q. Write briefly about cancer chemotherapy.

Q. Classification of anti-cancer drugs.

Q. Complications of cancer chemotherapy.

- Nitrogen mustard was the first anticancer drug to be found, followed by discovery of other agents. Anticancer drugs (cytotoxic agents) have a broader range of intracellular effects than radiotherapy.
- Cancer chemotherapeutic drugs can be classified by their mode of action.

Alkylating agents
- Melphalan, carmustine, chlorambucil, cyclophosphamide, cisplatin, busulphan, ifosfamide

Anti-tumor antibiotics
- Bleomycin, mitomycin, etoposide, doxorubicin and daunorubicin, mitoxantrone

Antimetabolites
- Methotrexate, 5-fluorouracil, cytarabine (cytidine)

Plant alkaloids
- Vincristine, vinblastine, docetaxel, paclitaxel

Hormones/hormone modifiers
- Steroids, antiandrogens (flutamide), antiestrogens (tamoxifene), aromatase inhibitors (letrozole)

Bilogic response modifiers
- Monoclonal antibodies (rituximab, trastuzumab), tyrosine kinase inhibitors (imatinib)

Combination Chemotherapy

- It overcomes drug resistance and limits the side-effects of different drugs.
- Combinations usually include drugs from different classes, each of which may be independently active and the combination of which should not have additive toxic effects.
- Each tumor has specific regimens that are used at various stages of the disease.

Administration

- Drugs are conventionally given by intravenous injection every 3 to 4 weeks, allowing enough time for the patient to recover from short-term toxic effects such as bone marrow suppression.
- Between four and eight such cycles of treatment are usually given in total.

Complications of Cancer Chemotherapy

- Most cytotoxics have a narrow therapeutic index. They cannot specifically target malignant cells. They have various effects on normal cells (especially rapidly dividing cells) which is responsible for their side effects.
- *Skin and tissue necrosis* is common if extravasation of the drug occurs during intravenous administration.
- *Nausea and vomiting*—this is the most common side-effect of chemotherapy. This can be prevented and treated by various antiemetic drugs such as ondansetron, domperidone, prochlorperazine, etc.
- *Bone marrow suppression*—almost all the agents cause bone marrow suppression which manifests as cytopenias. Marrow is susceptible because of high number of rapidly dividing cells. Leucopenia leads to various infections, thrombocytopenia leads to bleeding manifestations, and anemia leads to easy fatigability.

- *Diarrhea*—this is common with fluorouracil infusions. It responds to antimotility agents such as "high-dose" loperamide.
- *Mucositis*—irritation and inflammation of the mucous membranes may affect oral, anal mucosa, and also rest of the gastrointestinal tract. Mucositis is due to damage to the proliferating cells at the base of the mucosal squamous epithelia or in the intestinal crypts.
- *Alopecia*—most chemotherapeutic agents cause alopecia. Psychological support and the use of wigs can be encouraged.
- *Gonadal dysfunction*—cessation of ovulation and azoospermia occurs with most chemotherapeutic agents leading to infertility. Sperm banking before treatment may be considered to support patients likely to be sterilized by treatment.
- *Development of secondary malignancies*—especially leukemias can happen with alkylating agents.
- *Other side effects*—these include hemorrhagic cystitis with cyclophosphamide, peripheral edema with docetaxel, peripheral neuropathy with vinca alkaloids, cisplatin, etc.

Q. Write briefly about radiotherapy of cancer.

- Radiotherapy means the treatment of cancer with ionizing radiation. It can be curative or palliative. For localized cancers it may be curative. Source of ionizing radiation can be from the decay of a radioactive isotope (γ-rays) or produced by linear accelerators (X-rays).

Mechanism of Action

- Radiation is a physical form of treatment that damages any tissue in its path. Radiation causes breaks in DNA and generates free radicals from cell water that may damage cell membranes, proteins and organelles. Its selectivity for cancer cells is due to defects in a cancer cell's ability to repair sublethal DNA and other damage.
- Radiation damage is dependent on oxygen; hypoxic cells are more resistant.

Modes of Delivery of Radiation

- Total required dose of radiation is given in 20–30 fractions given daily, 5 days a week over 4–6 weeks. This allows normal cells to recover from radiation damage, but recovery is less in cancer cells.
- Radiation can be delivered by three methods:
  - *Teletherapy*—radiation is delivered from a distance by a linear accelerator.
  - *Brachytherapy* involves placing a source of radiation into or adjacent to the tumor. This allows the delivery of a very high localized dose of radiation. It is used in the management of localized cancers of the head and neck and cancer of the cervix and endometrium.
  - *Intravenous injection of a radioisotope*—iodine-131 is used to treat thyroid cancer and strontium 89 is used to treat bone metastases.

Indications for Palliative Radiotherapy

- Radiotherapy can be extremely useful for the alleviation of symptoms which are as follows:
  - Bone pain
  - Hemoptysis
  - Spinal cord compression
  - Superior vena caval obstruction
  - Brain metastases.

Side Effects of Radiotherapy

Acute

- Mucositis
- Skin erythema (ulceration in severe cases)
- Bone marrow toxicity

Late

- Hypothyroidism, cataracts and retinal damage after radiation to head and neck area.
- Brachial plexopathy, chronic constrictive pericarditis, and lung fibrosis after radiation to thoracic area.
- Shrinkage and fibrosis of the bladder after treatment for bladder cancer.
- Risk of secondary cancer induction.

15 Genetic Disorders

Q. What is genetics? Define the terms 'gene' and 'chromosome'.

- The word genetics comes from ancient Greek word "*genetikos*" meaning "*genitive*" and from 'genesis' meaning "*origin*". Genetics deals with the molecular structure and function of genes, and gene behavior in context of a cell or organism, patterns of inheritance from parent to offspring, and gene distribution, variation and change in populations.
- Gene is the name given to some stretches of DNA and RNA that code for a polypeptide or for an RNA chain that has a function in the organism. Living beings depend on genes, as they specify all proteins and functional RNA chains.
- *Chromosomes*: A chromosome consists of a single, very long DNA helix on which thousands of genes are encoded.

Q. Mutation.

- Mutation is defined as any change in the primary nucleotide sequence of DNA. Mutations may be lethal or of no functional consequence. Mutations can occur in the germline (sperm or oocytes) which can be transmitted to progeny or in somatic tissue after conception. Some somatic mutations are associated with neoplasia because they confer a growth advantage to cells.
- Acquired mutations in somatic cells are fairly common, but most mutations are rectified by repair mechanisms. Causes of increased mutation rate include: Ionizing and non-ionizing radiation, chemical mutagens. Loss of DNA repair enzymes increases mutation rate and susceptibility to cancer. Example is xeroderma pigmentosum (XP).

Types of Mutations

Point Mutations

- Mutations involving single nucleotides are referred to as *point mutations*. The change of one nucleotide for another, also called a substitution, is the most common type of mutation. Examples of diseases caused by point mutations are familial adenomatous polyposis and autosomal dominant polycystic kidney disease.

Insertions and Deletions

- Here one or more nucleotides are inserted or deleted in a DNA strand. This may result in abnormal splicing or alteration of the reading frame (frameshift mutation). Example is mutation in the cystic fibrosis gene.

Duplications

- Here, a region of DNA is duplicated. If an entire gene is duplicated, then the increased amount of gene product may have a deleterious effect. Example is hereditary motor and sensory neuropathy (HMSN type 1).

Triplet Repeat Mutations

- Here, the same triplet of nucleotides is repeated in a variable length of DNA. This type of mutation seen in many neurological diseases. Examples are spino-cerebellar ataxia and myotonic dystrophy.

Q. PCR (polymerase chain reaction).

- Polymerase chain reaction (PCR) can amplify any gene sequence for analysis by gel electrophoresis or by automated DNA sequencing.
- PCR can be used to amplify DNA from very small samples, including single cells. Blood samples, biopsies, surgical or autopsy specimens, or cells from hair or saliva can be analyzed by PCR. PCR can also be used to study mRNA. In this case, the enzyme reverse transcriptase (RT) is first used to convert the RNA to DNA, which can then be amplified by PCR.

Uses of PCR

- PCR is a key component of molecular diagnostics.
- It can be used to search for mutations.
- It is used in genetic linkage or association studies.
- PCR is increasingly used to diagnose various microbial pathogens.

Q. Human genome project.

- Human genome consists of 46 chromosomes (22 pairs of autosomal chromosomes and 1 pair of sex chromosomes). The human genome is estimated to contain ~30,000–40,000 genes.
- Human genome project (HGP) was an international project to decode all the DNA base pairs.
- This project began in 1990 and was completed in 2003. It has produced a reference database of sequence of human genome which is used worldwide in biomedical sciences. It is available to anyone on the internet.
- This database has been compiled by studying DNA obtained from many individuals. It has been found that only 1.5% of the total length of human genome encodes proteins and rest of the genome is junk DNA.

Benefits of Human Genome Project

- Knowledge of the effects of variation of DNA among individuals can revolutionize the ways to diagnose, treat and even prevent a number of diseases that affects the human beings.
- Many questions about the similarities and differences between humans and our closest relatives (the primates, and other mammals) are expected to be illuminated by the data from this project.
- Improved diagnosis of diseases.
- Gene therapy.
- Earlier detection of genetic predisposition to disease.
- Pharmacogenomics—customized drug therapy to target specific genetic composition to get better response with minimal side effects.

Q. Prenatal diagnosis.

Q. Prevention of genetic diseases.

- It is possible to diagnose *in utero*, many genetic disorders and congenital malformations before the middle of the second trimester. This is called prenatal diagnosis. If any abnormality is found genetic counseling and termination of pregnancy may be offered to parents.

Techniques Used in Prenatal Diagnosis

- Ultrasound
- Fetal blood sampling
- Fetoscopy
- Chorionic villus biopsy
- Amniocentesis
- Analysis of maternal serum.

Indications for Prenatal Diagnosis

- Advanced maternal age and a high-risk serum screening result.
- A previous child with a chromosome abnormality or a parent with a chromosome abnormality.
- A parent or child with a genetic disease for which testing is available.
- Abnormal antenatal scan.

Q. Genetic counseling.

- Genetic counseling refers to the process of communicating information about genetic risks.
- It is an essential part of the management of individuals and families with genetic disease.
- Genetic counseling can be provided by a medical geneticist, a specialist nurse counselor or obstetrician or pediatrician. The key requirement for genetic counseling is the provision of adequate time in a quiet place free of disturbance.
- An accurate clinical and molecular diagnosis is required for providing information to a family about the risk of developing and transmitting disease and methods for screening, diagnosis and prevention.
- Calculation of risk in a genetic disease is based on multiple factors and can be complicated. An empiric risk is based on observational data obtained from a population comparable to the one the patient is from (e.g. the empiric sibling recurrence risk for congenital heart disease is 2–3%).
- Strict patient confidentiality should be observed at all times and information from medical records obtained only with prior consent.

Aims of Genetic Counseling

- Establishing a diagnosis of genetic disease.
- Estimation of the risks to the individual and other family members.
- Provision of information and support.

Indications for Genetic Counseling

- A known or suspected hereditary disease in the patient or a family member.
- Maternal age of 35 years or older during a pregnancy.
- Teratogen exposure during pregnancy.
- Ethnic background associated with an increased prevalence of a heritable disorder.
- Presence of birth defects, chromosomal abnormality, or mental retardation in a parent, a child, or the child of a family member.
- Identification of one or more significant abnormalities during an antenatal ultrasound.
- Abnormal results on first or second trimester screening (e.g. Down syndrome, neural tube defects, trisomy 18).

Q. Proteome.

Q. Proteomics.

- The term "proteome" is derived from PROteins expressed by a genOME and refers to all the proteins produced by an organism just like genome refers to all the genes.
- Proteomics refers to study of protein expression in tissues, serum, and other biologic samples. Human body may contain more than 2 million proteins each having different functions. Compared to the study of DNA or RNA expression patterns, proteomics may provide a more accurate understanding of human diseases.
- Proteomics research will enhance our understanding of tumor biology, particularly the aberrant cellular signaling that characterizes malignant disease.
- Understanding the structure and function of each protein and the complexities of protein-protein interactions will be critical for developing the most effective diagnostic techniques.
- Proteomics will facilitate identification of potential novel biomarkers.
- Proteomics will play an important role in developing new drugs. For example, if a certain protein is implicated in a disease, its 3D structure provides the information to design drugs to interfere with the action of the protein.

Q. Epigenetics.

- The term epigenetics (*epi*= over; above genetics) refers to changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence.
- There are many non-genetic factors which cause the organism's genes to behave (or "express themselves") differently. An example of epigenetics is, a single fertilized ovum changing into many cell types including neurons, muscle cells, epithelium, blood vessels as it continues to divide.
- The molecular basis of epigenetics involves modification, inhibition and activation of certain genes, but not the basic structure of DNA. Additionally, the chromatin proteins associated with DNA may be activated or silenced.

Q. Classify genetic disorders with examples.

- Genetic disorders can be broadly divided into following categories:
- *Monogenic (Mendelian) disorders*—these are due to single gene defect.
- *Polygenic (multifactorial)*—these are due to interaction of multiple genetic factors and environment.
- *Chromosomal disorders*—these are due to abnormal number or structure of chromosomes.

Monogenic (Mendelian) Disorders

- Genetic disorders caused by a single gene abnormality are easiest to analyze and the most well understood. If expression of a trait requires only one copy of a gene (one allele), that trait is called dominant. If expression

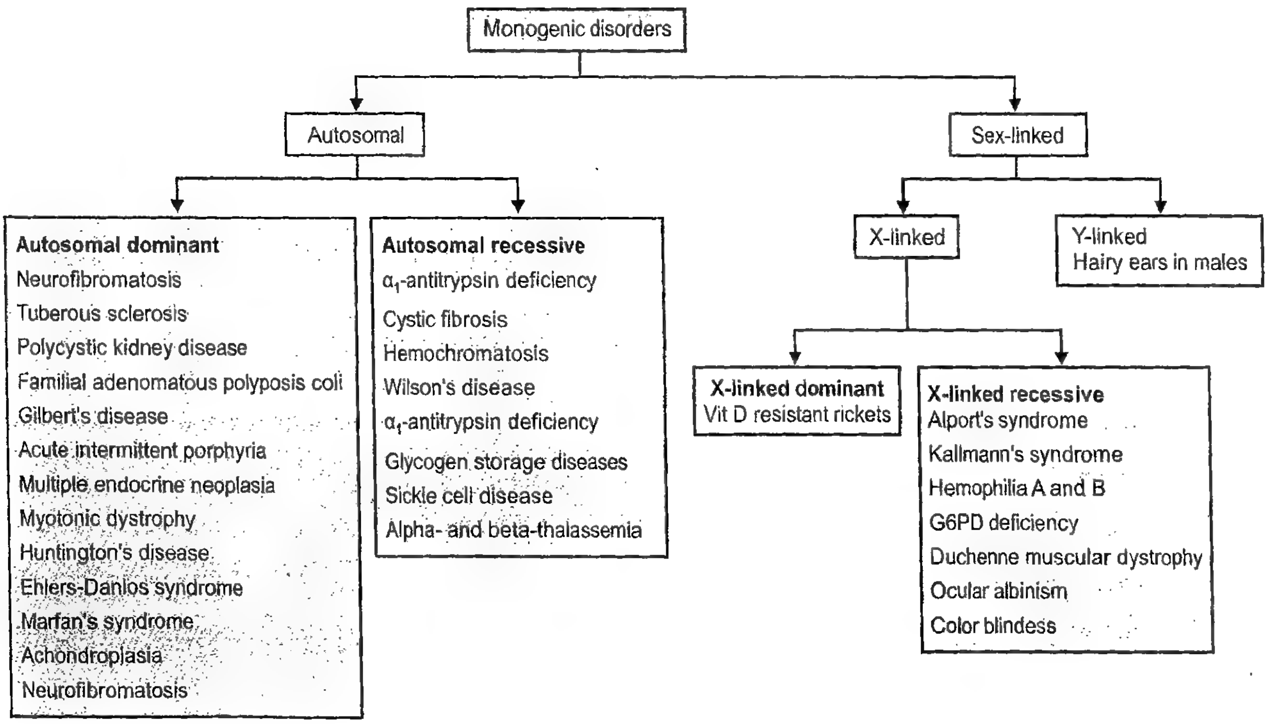


Fig. 15.1: Monogenic disorders

of a trait requires 2 copies of a gene (2 alleles), that trait is called recessive.

- However, X-linked disorders can be expressed in males even if the trait is recessive, because males have only one X chromosome and hence, there is no paired allele to offset the effects of abnormal allele on the X chromosome.

Autosomal Dominant Disorders

- Autosomal dominant disorders occur when there is mutation in even one allele of a gene. The affected person who has one normal and one abnormal allele is called heterozygous. If both alleles are affected then the person is said to be homozygous.
- Males and females are equally affected.
- Autosomal dominant disorders may result from mutations that cause an increase or decrease in function.
- There is a 50% risk that the child of an affected parent will be affected.
- Some persons who carry an abnormal gene may not have signs of the disease. This is due to reduced penetrance of the disease. Penetrance is all or none: Either the person has the disease or does not.

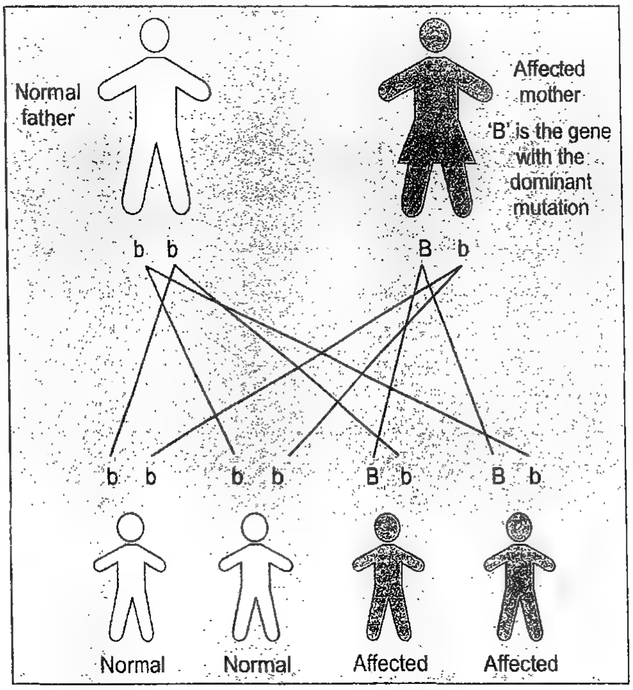


Fig. 15.2: Autosomal dominant disorder

Autosomal Recessive Disorders

- Autosomal recessive disorders are conditions that result from the presence of mutations in both alleles (homozygous) of a gene on an autosome. Those who have one normal and one abnormal allele (heterozygous) are carriers and do not suffer from the disease.
- Males and females are affected equally.
- Each offspring of two carriers has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither mutant allele. Thus, two-thirds of all clinically unaffected offspring are carriers.
- However, if one of the parent is affected with an autosomal recessive disease because both alleles are abnormal, then all the children will be carriers because each child will inherit one normal allele from the unaffected parent and one abnormal allele from the affected parent.
- Usually only one generation is affected.

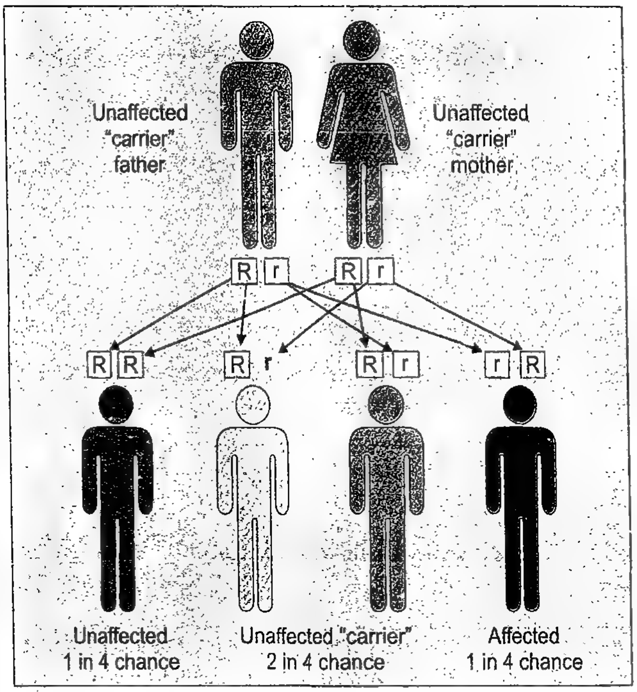


Fig. 15.3: Autosomal recessive disorder

X-linked Dominant Diseases

- Mutant gene is present X chromosome.
- Disease will manifest even if single X chromosome has abnormal gene, hence no carriers.
- Affected father cannot transfer the disease to son as the son's X chromosome is from mother. But affected father can transfer the disease to all daughters as the daughters get an abnormal X from the father.
- If mother is affected and father is normal, 50% of both sons and daughters are affected.
- In general males are more severely affected than females.

X-linked Recessive Diseases

- Mutant gene is present X chromosome.
- Affected father cannot transfer the disease to son as the son's X chromosome is from mother.

- It manifests only in males as they have only one X chromosome. It does not manifest in females because they have two X chromosomes one of which is normal. However, rarely females can also be affected, if they have only one X chromosome (Turner's syndrome) or one X chromosome is inactivated (lyonization).

Y-linked Disorders

- Only males are affected.
- Affected father transfers the disorder to all his sons but not to daughters.

Polygenic (Multifactorial) Disorders

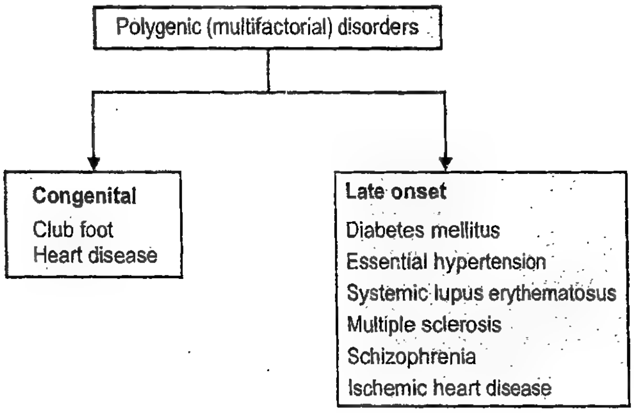


Fig. 15.4: Polygenic (multifactorial) disorders

Chromosomal Abnormalities and Disorders

- This term refers to major rearrangements in DNA structure which affect many genes. Chromosomal rearrangements are often visible when examining a karyotype under the microscope. Chromosomal disorders are very common and may affect more than half of all conceptions. However, most affected offspring spontaneously miscarry.
- Chromosomal abnormalities can be autosomal or sex-linked abnormalities.
- Both autosomal and sex-linked abnormalities can be of following two broad types:
  - Numerical abnormalities
  - Structural abnormalities.

Numerical Abnormalities of Autosomal Chromosomes

- Polyploidy—here, there is gain of one or more complete chromosome sets. This is not compatible with life. An example is the triploid chromosomal number (e.g. 69, XXY) in a partial hydatidiform mole.
- Aneuploidy—here, there is selective gain or loss of an individual chromosome.
  - Monosomy—loss of an autosome. This is lethal in males.
  - Trisomy—gain of one additional autosomal chromosome, e.g. Down's syndrome (trisomy 21; 47, XX/XY, +21), Patau's syndrome (trisomy 13; 47 XY, +13), Edward's syndrome (trisomy 18; 47 XY, +18).

Numerical Abnormalities of Sex Chromosomes

- Klinefelter's syndrome (47, XXY), Turner's syndrome (45, X0).

Structural Abnormalities of Chromosomes

- In structural abnormality, there is an alteration in the structure of one or more chromosomes due to translocations, deletions, duplications or inversions. Example is translocation between 9 and 22 chromosomes resulting in Philadelphia (Ph) chromosome causing CML.

Q. Down syndrome (mongolism).

- Most common chromosome abnormality among live born infants.
- It is due to three copies of chromosome 21 (trisomy 21) or a chromosome rearrangement that results in three copies of a region of the long arm of chromosome 21. This extra chromosome 21 is almost always maternally derived.
- Incidence—one in 1000 live births. Incidence increases with increasing maternal age.

Clinical Features

- Down syndrome affects multiple systems and causes both structural and functional defects.

General
- Short stature
- Obesity
- Single palmar crease (simian crease, in 50% of cases)
- Increased risk of sleep apnea.

Head and neck
- Brachycephalic small skull
- Short neck
- Small soft ears
- Hearing loss
- Short flat nose

Eyes
- Upslanting palpebral fissures with epicanthic fold at inner canthus (Mongolian eyes)
- Brushfield spots on the iris (small, white or gray spots on the periphery of the iris)
- Refractory errors
- Congenital cataract, glaucoma

CNS
- Mental retardation
- Autistic behavior

(contd.)

GIT
- Duodenal atresia
- Intestinal defects

CVS
- Congenital heart disease (especially VSD and atrioventricular canal defects)
- Increased risk of mitral valve prolapse and aortic regurgitation

Hematology
- Increased risk of leukemia
- Thrombocytopenia

Endocrine
- Diabetes mellitus
- Hypothyroidism

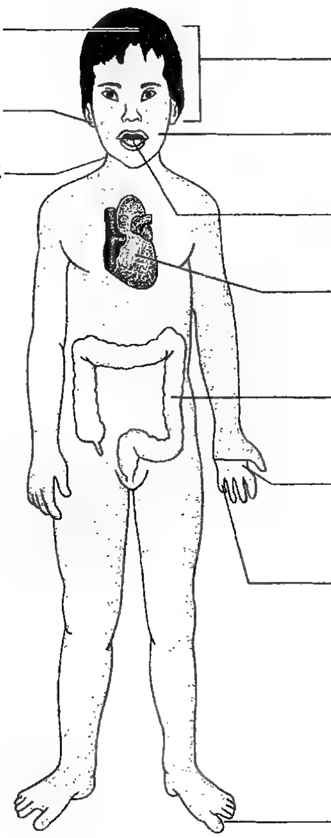


Fig. 15.5: Down syndrome

Investigations

- *Prenatal diagnosis*: Prenatal chorionic villus sampling and/or amniocentesis with karyotype analysis; free fetal DNA analysis of maternal blood sample; measuring maternal serum alpha-fetoprotein and by detecting increased nuchal thickness on fetal ultrasound.
- Karyotype analysis of the child will show trisomy 21.
- IQ testing.
- Echocardiogram to identify congenital heart disease.
- Ultrasound abdomen to identify duodenal atresia.
- Thyroid function tests to identify hypothyroidism.
- Hearing evaluations to identify deafness.
- Ophthalmology evaluation.
- Growth monitoring—height, weight, and head circumference plotted at each health visit using a Down syndrome growth chart.
- Other routine blood tests.

Treatment

- There is no treatment for the underlying disorder.
- If prenatal diagnosis suggests Down syndrome, genetic counseling and medical termination of pregnancy may be offered.
- Surgical treatment for duodenal atresia and congenital heart disease.
- Hypothyroidism is treated with thyroid hormone replacement.
- Other problems are treated as per standard guidelines.
- Provide social and educational support.
- No medical treatment has been proven to affect the intellectual capacity.

Q. Klinefelter's syndrome.

- Klinefelter's syndrome is the clinical manifestation of a male who has an extra X chromosome.
- The most common genotype is 47, XXY. Other genotypes are 48, XXXY and 46, XY/46, XXY mosaicism.
- Incidence—1 in 1000 live male births.

Pathophysiology

- The 47, XXY karyotype of Klinefelter's syndrome spontaneously arises when paired X chromosomes fail to separate (nondisjunction in stage I or II of meiosis, during oogenesis or spermatogenesis).
- The X chromosome carries genes that play roles in testis function, brain development, and growth. Extra X chromosome results in many physical and mental abnormalities. Phenotypic abnormalities are directly related to the number of supernumerary X chromosomes. Higher the number of supernumery X chromosome, more severe are the manifestations.
- Klinefelter's syndrome is a form of primary testicular failure, with low serum testosterone levels, and elevated gonadotropin levels due to lack of feedback inhibition of the pituitary gland. Low testosterone level causes poor development of male genitalia and male secondary sexual characters.

Clinical Features

- Patients are actually males who develop some feminine features due to extra X chromosome.

- Affected males are normal in appearance before puberty.
- After puberty, they develop disproportionately long legs and arms, and failure of growth of external genitalia. Penis and testes remain small.
- Testosterone deficiency causes sparse or absent facial, axillary, and pubic hair; decreased muscle mass and strength; gynecomastia; small testes and penis; diminished libido; decreased physical endurance; and osteoporosis.
- Infertility due to azoospermia.
- Increased incidence of mental retardation and behavioral abnormalities.

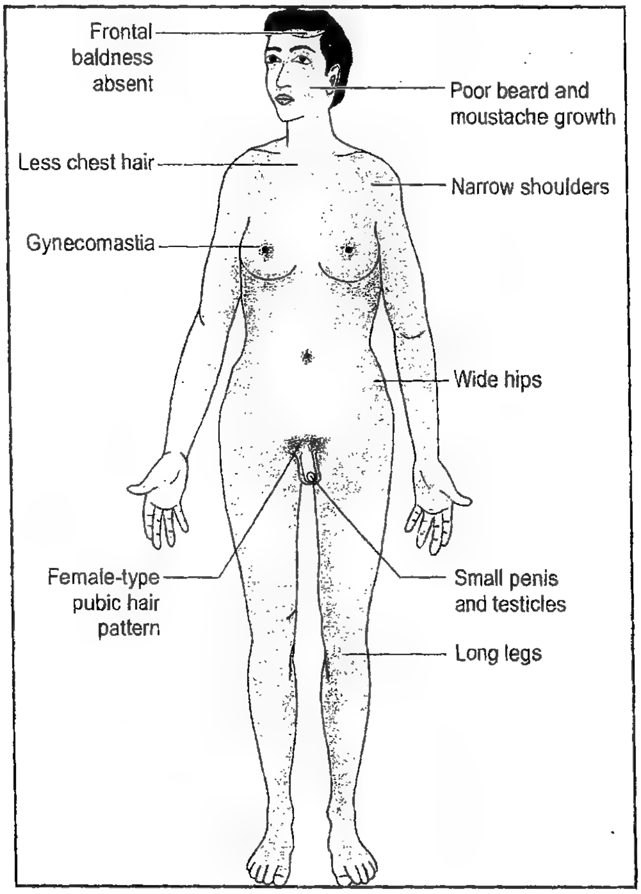


Fig. 15.6: Klinefelter's syndrome

Differential Diagnosis

- Klinefelter's syndrome has to be differentiated from other causes of male hypogonadism such as Kallmann syndrome, Noonan syndrome, Prader-Willi syndrome, cryptorchidism, panhypopituitarism, and other diseases causing testicular failure.

Investigations

- Low serum testosterone and elevated FSH and LH after puberty.
- Cytogenetic analysis will show 47, XXY. Diagnosis can also be made prenatally based on cytogenetic studies of fetus.

Treatment

- Testosterone should be given after puberty. It promotes normal growth of body and development of secondary sexual characteristics but will not restore fertility.

Q. Turner's syndrome (monosomy X; gonadal dysgenesis).

- Turner syndrome is due to loss of an X chromosome (45, X0).
- Most common sex-chromosome abnormality in female conceptions.
- Incidence—1:2000 to 1:4000 in live-born females.

Clinical Features

- Short stature.
- Primary amenorrhea, infertility.
- Poorly developed breast and other secondary sexual characters.
- Webbed neck.
- Broad shield like chest.
- Renal anomalies (horseshoe kidney).

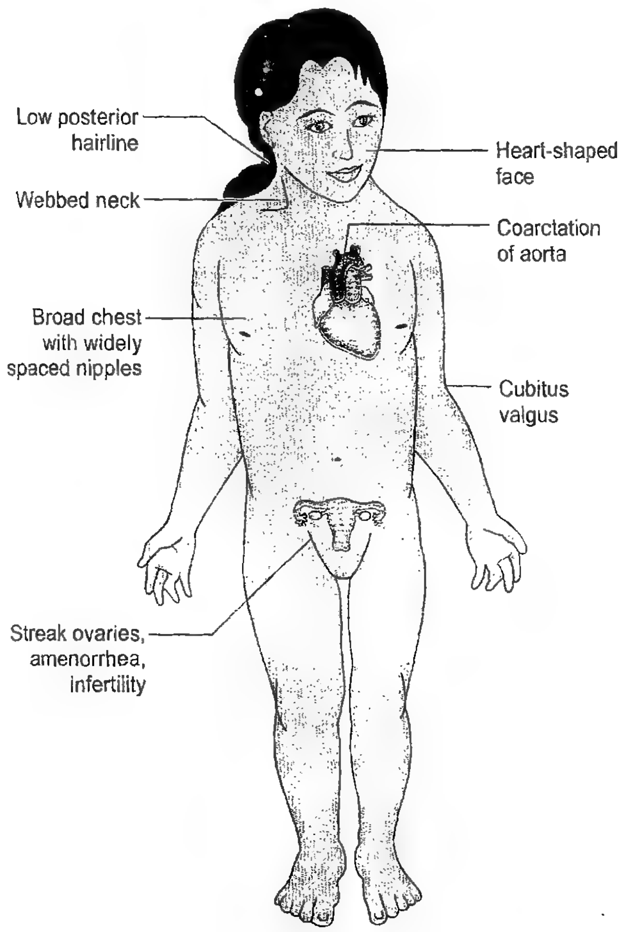


Fig. 15.7: Turner syndrome

- Coarctation of aorta.
- Cubitus valgus.
- High arched palate.
- Short 4th metacarpal or metatarsal.
- Peripheral lymphedema.
- Increased incidence of mental retardation.
- Increased risk of malignancy.

Investigations

- Cytogenetic analysis.

Treatment

- Prenatal diagnosis and offering of genetic counseling and termination of pregnancy.
- Surgical correction of cardiovascular anomalies.
- Estrogen therapy to induce and maintain sexual development and cyclic uterine bleeding.
- Growth hormone/oxandrolone therapy for short stature.

Q. Gene therapy.

- Gene therapy is the insertion of a functioning gene (recombinant DNA) into the cells of a patient to correct a disease.
- Gene therapy is one of the most powerful concepts in modern medicine and has the potential to address a host of diseases for which there are currently no cures. However, gene therapy is still in the stage of clinical trials and not yet come into clinical practice.
- Germline gene therapy is the permanent introduction of DNA into germ cells, allowing passage into offspring that could result in new or altered traits in the population. It is banned globally as unethical.
- Somatic gene therapy refers to genetic modification of different somatic cells. This is potentially possible in all accessible somatic cells (e.g. blood, skin, muscle, endothelial cells, etc.).

Procedure of Gene Therapy

- *Gene transfer involves three elements*: (1) a vector, (2) a gene to be delivered, and (3) a target cell to which the gene is delivered. The series of steps in which the donated gene enters the cell and begins expression is referred to as transduction.
- Since genes (DNA or RNA) cannot be directly transferred into a cell, it is done by using a vector, or gene delivery vehicle.
- Gene delivery can be done by using viruses, liposomes or plasmids to carry the therapeutic gene to target cells.
- Viral vehicles are most popular way of delivering the genes to target cells. They are prepared by deleting some or all of the viral genome and replacing it with the therapeutic gene of interest. Many viruses such as retroviruses, lentiviruses, adenovirus, adeno-associated virus (AAV), herpes simplex virus, and sarcoma virus have been found to be useful as vectors. Recombinant AAV (adeno-associated virus) has especially emerged as attractive gene delivery vehicle. Engineered from a small replication-defective DNA virus, they are devoid of viral coding genes and do not cause any illness in experimental animals.
- Gene therapy can be *in vivo*, in which the vector is directly injected into the patient or, *ex vivo* in which target cells are removed from the patient and returned to the patient after gene transfer in the laboratory.

Diseases with Potential for Gene Therapy

Genetic Disorders

- Here the missing or defective gene is replaced. Examples are hemophilia A, sickle cell disease, Duchenne muscular dystrophy, X-linked severe combined immunodeficiency disease (SCID), Wiskott-Aldrich syndrome and cystic fibrosis.

Cancer

- Many strategies are used in cancer gene therapy which are as follows:
  - Intratumoral injection of an adenoviral vector expressing the thymidine kinase (TK) gene. Cells which take up and express the TK gene are killed after the administration of gancyclovir, which is phosphorylated to a toxic nucleoside by TK.
  - Use of adenoviral-mediated expression of the tumor suppressor gene p53.
  - Use of oncolytic viruses that selectively replicate in tumor cells and destroy them but not in normal cells.
  - Promotion of recognition of tumor cells by the immune system by transduction of tumor cells with immune-enhancing genes.
  - Inhibition of tumor angiogenesis by enhancing the expression of angiogenesis inhibitors such as angiostatin and endostatin.
  - Protection of normal cells from the toxicities of chemotherapy by transduction of cells with genes encoding resistance to chemotherapeutic agents.

Cardiovascular Disease

- Strategies include induction of angiogenesis in limbs (in limb ischemia) or cardiac muscle (in angina/myocardial ischemia). The major transgene used has been vascular endothelial growth factor (VEGF), because of its specificity for endothelial cells. The design of most of

the trials involved direct IM (or myocardial) injection of either a plasmid or an adenoviral vector expressing the transgene.

Neurodegenerative Disorders

- In Parkinson's disease, AAV vectors expressing enzymes required for enhanced synthesis of dopamine have been introduced into affected areas of the brain (striatum, subthalamic nucleus) by stereotactic neurosurgery.
- In Alzheimer's disease, autologous fibroblasts are transduced with a retroviral vector expressing nerve growth factor, and then reimplanted into the basal forebrain.

Problems with Gene Therapy

- Immune response against viral vectors making them ineffective.
- Short-term expression of the gene by cells or limited transduction of cells by vectors.
- Potential for producing disease by recombining with other viruses or getting activated by host genes.
- Activation of protooncogenes leading to secondary cancers such as leukemia.

Q. Human leukocyte antigen (HLA) system.

- The human leukocyte antigen (HLA) system is synonymous with the human major histocompatibility complex (MHC).
- These terms describe a group of genes on short arm of chromosome 6 that encode a variety of cell surface markers, antigen-presenting molecules, and other proteins involved in immune function.
- MHC antigens are integral to the normal functioning of the immune response. Essential role of HLA antigens lies in the control of self-recognition and thus defence against microorganisms and surveillance.
- The HLA region has been subdivided into three regions—class I, class II, and class III.
- Class I—A,B,C is the most important region for transplantation (other loci, e.g. E, F, G, H, etc. are not so important in transplantation). Class I antigens are expressed on most nucleated cells, have soluble form in plasma and are adsorbed onto platelets (some antigens more readily than others). Class I molecules are assembled within the cell and ultimately sit on the cell surface with a section inserted into the lipid bilayer of the cell membrane and a short cytoplasmic tail where they present antigen in the form of peptide to cytotoxic T (CD8+) cells.
- *HLA class II region is further divided into five loci*: DR, DQ, DP, DM and DO. Out of these HLA DR, DQ, DP region is most significant. HLA class II antigens are expressed on B-lymphocytes, activated T-lymphocytes, macrophages, and endothelial cells (i.e. immune competent cells). HLA class II molecules present antigen in the cleft to helper T (CD4+) cells. Thus, class II presentation involves the helper-function of setting up a general immune reaction involving cytokine, cellular and humoral defence. The role of class II in initiating a general immune response is why they only need to be present on immunologically active cells.
- *Class III region*: The region in between class I and class II is known as the class III region. Although this region does not contain any of the HLA genes, it does contain many genes of importance in the immune response. They encode for many molecules such as complement (C_2, C_4, and factor B), tumor necrosis factor and heat shock protein.

HLA Typing Methods

- Serology used to be the 'gold' standard. Now being superseded by molecular techniques.
- Cellular methods rarely used now. Orginally used for Class II typing.
- Molecular methods are now becoming the method of choice.

Functions of HLA System

In Infectious Disease

- When a foreign pathogen enters the body, antigen-presenting cells (APCs) phagocytize the pathogen. Proteins from the pathogen are digested into small pieces (peptides) and loaded onto HLA antigens (to be specific, MHC class II). They are then displayed by the antigen-presenting cells to T cells, which then produce a variety of effects to eliminate the pathogen.
- Through a similar process, proteins (both native and foreign, such as the proteins of virus) produced inside most cells are displayed on HLAs (to be specific, MHC class I) on the cell surface. Infected cells can be recognized and destroyed by CD8+ T cells.

In Graft Rejection

- Any cell displaying some other HLA type is "non-self" and is seen as an invader by the body's immune system, resulting in the rejection of the tissue bearing those cells.

In Autoimmunity

- People with certain HLA antigens are more likely to develop certain autoimmune diseases, such as type I

diabetes, ankylosing spondylitis, celiac disease, SLE (systemic lupus erythematosus), myasthenia gravis, inclusion body myositis and Sjögren's syndrome.

In Cancer

- Some HLA-mediated diseases are directly involved in the promotion of cancer. For example, gluten-sensitive enteropathy is associated with increased prevalence of enteropathy-associated T cell lymphoma.

Q. Immune deficiency disorders.

There are two general types of immune deficiency.

Primary

- Result from some genetic or developmental defect. Manifestations are seen in infants and young children.

Acquired

- Develop as a direct consequence of some other recognized cause. For example, HIV infection.

Classification of Primary Immunodeficiency Disorders

1. Humoral (antibody) defects: Quantitative or qualitative defects in antibody production. Account for more than 50% of defects.
- Selective IgA deficiency (SIgAd). Most common humoral deficiency.
- Common variable immunodeficiency (CVID)
- X-linked agammaglobulinemia (XLA)
- Selective IgG subclass deficiency (SIgGsd)
- Hyper IgM syndrome (HIgM)
- Transient hypogammaglobulinemia of infancy (THI)
- Functional antibody deficiency.

2. Cellular defects: Usually combined with humoral; account for 20–30%.
- Combined immunodeficiency (CID)
- Severe combined immunodeficiency (SCID)
- Ataxia-telangiectasia syndrome (AT)
- Wiskott-Aldrich syndrome (WAS)
- DiGeorge syndrome
- Chronic mucocutaneous candidiasis (CMCC).

3. Combined humoral and cellular immunity defects

4. Phagocytic disorders: Defects in migration, or killing; account for ~18%.
- Chronic granulomatous disease (CGD)
- Leukocyte adhesion defect (LAD)
- Chédiak-Higashi syndrome (CHS)
- Swhachman syndrome (Swh. syndrome)
- Hyper IgE syndrome (Job syndrome).

5. Complement deficiencies: Account for ~2%.
- Isolated deficiencies of complement components or inhibitors and may be hereditary or acquired.

Q. How do you approach a case of suspected immune deficiency disorder?

When to suspect immune deficiency?

- Immunodeficiency should be suspected when recurrent infections occur with the following characteristics:
  - Severe
  - Complicated
  - In multiple locations
  - Resistant to treatment
  - Caused by unusual organisms
  - Affect many family members
  - Unusual host response to usual organism.
- Most of the infections involve upper respiratory (sinusitis, otitis media), lower respiratory tract (bronchitis, pneumonia) and GIT (gastroenteritis).
- Age when recurrent infections began can give clue about underlying immune defect.
- Onset before age 6 months suggests a T cell defect because maternal antibodies are usually protective for the first 6 to 9 months.
- Onset between the age of 6 and 12 months may suggest combined B and T cell defects or a B cell defect, which becomes evident when maternal antibodies are disappearing (at about age 6 months).
- Onset after 12 months of age suggests a B cell defect or secondary immunodeficiency.

Physical Examination

- Patients may appear normal or there may be growth retardation due to recurrent infections.
- Gingivitis, dental erosions, signs of sinusitis.
- Cervical lymph nodes, adenoid and tonsillar tissue are typically very small or absent in X-linked agammaglobulinemia, X-linked hyper-IgM syndrome, and severe combined immunodeficiency (SCID).
- Ataxia, telangiectasia and neurodeficits are seen in ataxia-telangiectasia.
- Eczema and petechiae (Wiskott-Aldrich syndrome).
- Oculocutaneous albinism (Chédiak-Higashi).
- Dermatomyositis-like rash (XLA).
- Chronic dermatitis (hyper-IgE).
- Generalized molluscum, extensive warts, candidiasis (T cell defects).

Laboratory Evaluation

- CBC with differential count
- Total WBC, ANC, ALC, AEC (age-appropriate values)
- Lymphopenia = <3,000 in infants, <1500 in children and adults

Tests for Humoral Immunity

- Quantification of IgG, IgA, IgM level. Order IgE only if severe atopy, or chronic dermatitis.
- Isohemagglutinin titers (antibodies to blood group antigens).
- Antibody response to vaccine antigens (e.g. *Haemophilus influenzae* type b, tetanus, diphtheria, pneumococcal, and meningococcal antigens). If low titers, give booster, then repeat titers 4 weeks later.

Tests for T Cell Function

- Absolute lymphocyte count.
- Delayed hypersensitivity skin tests (e.g. using candida): Should produce redness and induration of >5 mm by 48–72 hours.
- HIV testing.

Tests for Phagocytic Function

- Adhesion antigens by flow cytometry (CD11/CD18)—checks for adhesion defects.
- Chemiluminescence—checks phagocytic killing power.

Tests for Complement Function

- C3 level, C4 level, CH50 activity (for total activity of the classical pathway) and AH50 activity (for total activity of the alternate complement pathways).
- C1 inhibitor level and function.

Treatment

General

- Avoid infections.
- Prompt recognition of infection and aggressive treatment.
- Obtain cultures, and initiate early empiric antibiotic therapy for suspected pathogens.
- Prophylactic antibiotics for patients with significant T-cell defects (example, trimethoprim-sulfamethoxazole daily to prevent *Pneumocystis jiroveci* infection).
- Do not give live vaccines to children with T cell defects.
- Only irradiated, leukocyte reduced, virus-free blood products should be given.
- Monitor growth and weight gain diligently.

Definitive Treatment for Primary Immune Deficiencies

- Hematopoietic stem cell transplantation.
- Immunoglobulin replacement.
- Gene therapy in cases of specific gene defect.

Q. Discuss briefly some of the humoral (antibody) defects.

IgA Deficiency

- Most common primary immunodeficiency.
- Incidence 1:400 to 1:800.
- Many patients are asymptomatic.
- Recurrent mucosal infections involving GIT, genitourinary tract and respiratory tract.
- Serum IgA level <7 mg/dl with normal IgG and IgM levels.
- Increased risk of autoimmune disorders (e.g. celiac disease, inflammatory bowel disease, SLE, chronic active hepatitis).
- May evolve into CVID.
- Treatment involves antibiotic prophylaxis.
- Intravenous immunoglobulin infusion is not useful as it contains only IgG.

Common Variable Immunodeficiency

- Recurrent sinopulmonary infections with usual pathogens.
- Age of onset 15–35 years. Equal male : female incidence.
- Low IgG and poor antibody responses to immunizations.
- Low levels of IgM and IgA.
- Increased risk for autoimmune diseases and malignancy.
- B cells phenotypically normal.
- Treatment involves prophylactic IVIG once a month and antibiotics for infections.

X-linked Agammaglobulinemia

- Defect in Bruton tyrosine kinase (Btk) gene on X chromosome → abnormal B cells.
- Well for first 6–9 months.
- Recurrent infections with pneumococcus, *H. influenzae*, Giardia.
- Minimal tonsillar tissue, and no palpable lymph nodes.
- Decreased levels of IgG, IgA, IgM, IgE and absent B cells.
- Genetic testing can be used to confirm the diagnosis but is not required. It is usually recommended for 1st-degree relatives.
- Treatment involves prophylactic IVIG once a month and antibiotics for infections. Live-virus vaccines are contraindicated.

Selective IgG Subclass Deficiency

- Selective antibody deficiency is characterized by deficient antibody response to polysaccharide antigens but not to protein antigens. Immunoglobulin level is normal including IgG subclasses.
- Patients have recurrent sinopulmonary infections.
- Diagnosis is by measuring immunoglobulin levels (IgG, IgA, IgM, and IgG subclasses) and responses to polysaccharide vaccines (e.g. pneumococcal vaccine).
- Treatment involves giving pneumococcal conjugate vaccine, prophylactic antibiotics and sometimes IV immunoglobulin (IVIG).

Hyper-IgE Syndrome

- It is a combined B and T cell immunodeficiency.
- Chronic pruritic dermatitis.
- Recurrent Staph infections of skin, lungs, joints, and dental infections.
- Course facial features.
- Markedly elevated IgE and eosinophilia.
- Treatment involves lifelong prophylactic antistaphylococcal antibiotics (usually trimethoprim/sulfamethoxazole). Life-threatening infections are treated by interferon gamma. Dermatitis is treated with emollient creams and antihistamines.

Q. Discuss briefly some of the cellular (T cell) immunity deficiency disorders.

Severe Combined Immunodeficiency

- Most cases are autosomal recessive.
- Characterized by absent T cells and a low or normal number of B cells and natural killer cells.
- Recurrent infections by three months. Can be life-threatening. Common organisms are Candida, PCP, cryptosporidiosis, HSV, RSV, rotavirus, adeno, entero, EBV, and CMV.
- There is absence of lymphoid tissue, low or absent T cells, absent thymic shadow, and absent lymphocyte proliferative responses to mitogens.
- Treatment involves prophylactic IVIG and antibiotics. Hematopoietic stem cell transplantation should be considered early.

Ataxia-Telangiectasia

- Ataxia-telangiectasia results from a DNA repair defect that frequently results in humoral and cellular deficiency. Inheritance is autosomal-recessive.
- It causes progressive cerebellar ataxia, oculocutaneous telangiectasias, and recurrent sinopulmonary infections.
- Telangiectasias appear between 3 and 6 years.
- Ataxia appears soon after learning to walk, in wheelchair by 10–12 years.
- Often low or absent IgA. Varaible depressions of other immunoglobulins.
- Risk of developing malignancy is high.
- Treatment involves prophylactic antibiotics or IV immunoglobulin.

Wiskott-Aldrich Syndrome

- It is characterized by combined B and T cell defects, recurrent infections, atopic dermatitis and thrombocytopenia. Inheritance is X-linked recessive.
- Thrombocytopenia → bleeding
- Recurrent infections with encapsulated bacteria, especially pneumococcus.
- Variable antibody levels. Often low IgM, high IgA and IgE. Poor antibody finction.
- Low to low—normal T cells.
- Treatment involves prophylactic IVIG, antibiotics, and platelet transfusion for severe thrombocytopenia. Hematopoietic stem cell transplantation can also be considered.

DiGeorge Anomaly

- DiGeorge syndrome is thymic and parathyroid hypoplasia or aplasia leading to T cell immunodeficiency and hypoparathyroidism.
- Hypoparathyroidism → hypocalcemia → seizures.
- Susceptibility to fungi, viruses, PCP.
- T cells variable in number, abnormal mitogen studies.
- Normal to increased B cells, normal antibody levels.
- Associated heart defects, facial anomalies, esophageal atresia.
- Treatment involves calcium and vitamin D supplementation, transplantation of cultured thymus tissue or hematopoietic stem cells.

Q. Discuss briefly some of the phagocytic defects.

Cyclic Neutropenia

- Rare congenital disorder, usually transmitted in an autosomal dominant fashion.
- Regular, periodic oscillation in the number of peripheral neutrophils.
- Neutropenia every 3 weeks.
- May develop fever, stomatitis, pharyngitis, pneumonia, occasionally sepsis and death.
- Cycles become less noticeable with age.
- May spontaneously abate.

Leukocyte Adhesion Defect

- Leukocyte adhesion deficiency is caused by deficiency of adhesive glycoproteins on the surfaces of WBCs. This affects WBC migration and phagocytic ability.
- 1 in 10 million incidence.
- Striking neutrophilia.
- Recurrent bacterial and fungal infections without pus.
- Severe gingivitis, periodontitis, alveolar bone loss.
- Decreased or absent CD18/CD11 by flow cytometry.
- Delayed separation of umbilical cord.

- Treatment involves prophylactic antibiotics, granulocyte transfusions and hematopoietic stem cell transplantation.

Chronic Granulomatous Disease

- Here, WBCs do not produce hydrogen peroxide, superoxide, and other activated O_2 compounds because NADPH oxidase enzyme activity is deficient. Thus, bacteria and fungi are not killed despite normal phagocytosis.
- Recurrent abscesses, lymphadenitis, or osteomyelitis at multiple sites.
- Unusual infections with catalase positive organisms: Staph, Serratia, Aspergillus, Candida, Salmonella, gram-negative bacteria.
- Multiple granulomatous lesions occur in the lungs, liver, lymph nodes, and GI and GU tract.
- Treatment involves prophylactic antibiotics, granulocyte transfusions and hematopoietic stem cell transplantation.

Chediak-Higashi Syndrome

- It is characterized by impaired lysis of phagocytized bacteria, resulting in recurrent bacterial respiratory and other infections and oculocutaneous albinism.
- Frequent infections of skin, mucous membranes, respiratory tract with gram-negative, gram-positive organisms and fungi.
- Large inclusions in all nucleated blood cells.
- Accelerated lymphoma-like syndrome can occur with non-neoplastic infiltration of liver, spleen, and lymph nodes associated with recurrent infections and death.
- Treatment involves prophylactic antibiotics, interferon gamma and sometimes corticosteroids. Hematopoietic stem cell transplantation is another option.

Q. Antioxidants.

- Oxygen is an element indispensable for life. When cells use oxygen to generate energy, free radicals are created as a consequence of ATP production by the mitochondria. These by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS). These species can be either harmful or helpful to the body. ROS and RNS are generated from either endogenous or exogenous sources. Some internal sources of these species are: Mitochondria, xanthine oxidase, Fenton reaction, phagocytes, inflammation, ischemia, etc. Many external sources of free radicals and oxidants include: Pollutants, cigarette smoke, radiation, medication, etc.
- At low or moderate levels, free radicals and oxidants exert beneficial effects on cellular responses and immune function. At high concentrations they generate oxidative stress, a deleterious process that can damage cell structures, including lipids, proteins, and DNA.
- Oxidative stress plays a major part in the development of chronic and degenerative ailments such as cancer, autoimmune disorders, rheumatoid arthritis, cataract, aging, cardiovascular and neurodegenerative diseases, etc.

Antioxidants

- The body has several mechanisms to counteract oxidative stress by producing antioxidants, either naturally generated in situ (endogenous antioxidants), or externally supplied through foods (exogenous antioxidants). The roles of antioxidants are to neutralize the excess of free radicals, to protect the cells against their toxic effects and to contribute to disease prevention.
- Endogenous compounds in cells can be classified as enzymatic antioxidants and non-enzymatic antioxidants.
- The major antioxidant enzymes directly involved in the neutralization of ROS and RNS are: Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase.
- Nonenzymatic antioxidants include vitamins A, C, E, uric acid, etc.

Uric Acid

- Uric acid is by-far the highest concentration antioxidant in human blood. Uric acid (UA) is produced from xanthine by the enzyme xanthine oxidase, and is an intermediate product of purine metabolism. Studies of high altitude acclimatization show that urate mitigates the oxidative stress caused by high-altitude hypoxia. Serum UA levels are inversely associated with the incidence of multiple sclerosis in humans. Moreover, the administration of UA is therapeutic in experimental animal model of multiple sclerosis.

Vitamin A

- Vitamin A supplementation as been shown to reduce the incidences of leukoplakia, lung cancer, fewer episodes of respiratory tract infections in children. Vitamin A levels were found to be lower in patients with measles, Alzheimer's disease, etc.

Ascorbic Acid (Vitamin C)

- Ascorbic acid is redox catalyst which can reduce, and thereby neutralize reactive oxygen species such as hydrogen peroxide. There are many studies showing the beneficial effects of vitamin C in conditions such as infertility, mood disorders, longevity, cataract formation, blood pressure, etc.

Vitamin E

- Vitamin E is the collective name for a set of eight related tocopherols and tocotrienols, which are fat-soluble vitamins with antioxidant properties. Of these, α-tocopherol is the most important. α-tocopherol protects membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. Many studies have documented the benefits of vitamin E supplementation in reducing the symptoms of intermittent claudication, rheumatoid arthritis, and parkinsonism. It has also been shown to reduce the incidence of cataract formation and enhances immune response.

Glutathione

- Glutathione is a cysteine-containing peptide and is synthesized in the body. Glutathione has antioxidant properties since the thiol group in its cysteine moiety is a reducing agent and can be reversibly oxidized and reduced.
- In cells, glutathione is maintained in the reduced form by the enzyme glutathione reductase.
- Due to its high concentration and its central role in maintaining the cell's redox state, glutathione is one of the most important cellular antioxidants.

Melatonin

- Melatonin is a powerful antioxidant. Melatonin easily crosses cell membranes and the blood–brain barrier. Melatonin, once oxidized, cannot be reduced to its former state because it forms several stable end-products upon reacting with free radicals. Therefore, it has been referred to as a terminal (or suicidal) antioxidant.

Should we Routinely Prescribe/Take Antioxidants?

- Antioxidants are being studied as treatments for stroke and neurodegenerative diseases.
- Antioxidants are widely used in dietary supplements and have been investigated for the prevention of diseases such as cancer, coronary heart disease and even altitude sickness.
- Although initial studies suggested that antioxidant supplements might promote health, later large clinical trials with a limited number of antioxidants detect no benefit and even suggested that excess supplementation may be harmful.
- An advisory statement published by the American Heart Association says that there is no good reason for people to take antioxidant supplements. This conclusion was reached by the AHA's nutrition committee after an extensive review of the medical literature.

Q. What is geriatrics? Discuss the effects of aging on various organ systems.

- Geriatrics is a sub-speciality of internal medicine and family medicine that focuses on health care of elderly people.
- It aims to promote health by preventing and treating diseases and disabilities in older adults.
- Geriatrics differs from standard adult medicine because it focuses on the unique needs of the elderly person.
- The aged body is different physiologically from the younger adult body, and during old age, the decline of various organ systems become manifest.

Effects of Aging on Specific Organs and Systems

Cardiovascular System

- Atherosclerosis.
- Age-associated vascular stiffness predisposes to left ventricular stiffness, impaired diastolic filling, and the clinical syndrome of diastolic heart failure.
- Atrial fibrillation.
- Postural hypotension.

Respiratory System

- Stiffening of chest wall.
- Loss of the elastic recoil of lungs.
- At the alveolar level, the capacity to exchange oxygen and carbon monoxide decreases by approximately 50% between the ages of 30 and 65 years.
- Pulmonary reflexes such as coughing and ciliary function decrease, predisposing elderly individuals to the pooling of secretions.

Gastrointestinal System

- Age-related changes in the mouth include slower production of dentine, shrinkage of the root pulp, and decreasing bone density of the jaw.
- Taste and smell decline progressively with advancing age, with rising thresholds for tasting salt, sweetness, and certain proteins. The overall net effect is that food may taste more bitter, and more sugar is required before something tastes sweet.
- The strength of esophageal muscle contraction declines, and peristaltic waves slow with advancing age. There is also a tendency for the lower esophageal sphincter to become lax.
- The gastric mucosa secretes less acid with advancing age. delayed gastric emptying is a feature of aging, leading to a sense of false or early satiety, which can impair subsequent food ingestion.

- Liver weight declines, because of the loss of hepatocytes.
- Significant reduction in small intestinal surface area. Colonic function declines with advancing age. Stool frequency tends to decline, and hardness of stools seems to increase with advancing age.

Renal and Urinary Excretory System

- Overall kidney size declines by approximately one third, and blood flow through the kidney declines by about 1% per year.
- The bladder tends to become more irritable with advancing age and may generate less power during contraction. Prostate gland enlargement leads to urinary voiding problems.

Endocrine System

- Growth hormone levels fall with advancing age.
- The production rates and clearance rates of thyroxine, triiodothyronine, and calcitonin seem to be constant with advancing.
- The adrenal glands maintain their ability to secrete cortisone with advancing age. Renin and aldosterone secretion rates decline progressively with advancing age and do not contribute to the increased rates of hypertension with advancing age.
- The insulin content of the elderly pancreas is increased, but the release of insulin in response to stimulation may be blunted with advancing age. There is also a concomitant decline in insulin clearance with advancing age.
- The ovaries show dramatic declines in estrogen and progesterone as fibrosis and scarring occur. Levels of testosterone decrease in some men beginning around 50 years, but declines do not seem to affect the potency of semen. Sexual function is relatively well preserved.

Hematopoietic System

- There is minimal or no change in basal hematopoiesis
- The aging hematopoietic system is less able to respond to increased demands.
- Neutrophils from elderly individuals show less prekilling activity and lower levels of lysozyme.

Musculoskeletal System

- Bone mass and density decrease with age after reaching maximum in the 20s.
- Tendons and ligaments become less elastic with advancing age, contributing to a higher incidence of rupture, especially of the Achilles tendon, in older individuals.
- By 70 years of age, muscle mass declines by approximately 25% for men and women unless it is offset by exercise.

Nervous System

- Brain size decreases with advancing age: after the age of 60 years, its size declines by 5 to 10%.
- Aging is associated with a progressive decline in the synthesis of neurotransmitters and a decline in their corresponding receptors.
- The farsightedness of aging is caused by the diminished ability of the lens to focus on nearby objects because of its thickening and stiffening.
- Hearing loss.
- Sleep patterns change.

Skin Changes

- Thinning of the subcutaneous tissue.
- Diminished sweating, hair loss.
- The epidermis and dermis adhere less tightly.
- Wound repair rates are significantly prolonged.

Implications of Aging Changes to Health Care Provider

- The decline in physiological reserve in organs makes the elderly develop some kinds of diseases and have more complications from mild problems (such as dehydration from a mild gastroenteritis). Multiple problems may compound: A mild fever in elderly persons may cause confusion, which may lead to a fall and to a fracture of the neck of the femur.
- Elderly people require specific attention to medications. Elderly people particularly are subjected to polypharmacy (taking multiple medications). This polypharmacy may result in many drug interactions and may cause adverse drug reactions. Drugs are excreted mostly by the kidneys or the liver, either of which may be impaired in the elderly.
- The presentation of disease in elderly persons may be vague and non-specific or it may include delirium or falls. For example, pneumonia may present with low-grade fever, dehydration, confusion or falls, rather than the high fever and cough seen in middle-aged adults.

Assessment of Elderly

- A thorough geriatric assessment should include the following areas: Vision, hearing, nutrition, continence, mobility and balance, medications, cognitive status, affect, functional status, social support, and advance directives.

Q. Discuss the common geriatric problems and their treatment.

Vision Changes

- Vision loss increases with advancing age, and more than one-quarter of those older than 85 years report marked visual impairment. More than 90% of the elderly wear eyeglasses.

Causes of Vision Loss in Elderly

- The most common eye problem in the elderly is presbyopia, difficulty with close focus. Presbyopia is the result of decreased lens flexibility, which occurs with aging.
- Cataracts.
- Glaucoma.
- Macular degeneration.
- Diabetic or hypertensive retinopathy.

Treatment

- Presbyopia is treated with corrective lenses.
- Cataract is treated by removal of the opaque lens followed by artificial lens implantation.
- Glaucoma is treated by medications (pilocarpine drops, timolol drops and acetazolamide) or surgery such as laser trabeculectomy.
- Macular degeneration is treated by devices to assist vision, such as increased lighting and magnifying lenses.

Hearing Changes

- The prevalence of hearing loss, especially of high frequencies (presbycusis), increases markedly among persons older than 65 years and approaches 50% in those older than 80. Presbycusis is typically bilateral and associated with a high-frequency hearing loss.
- The cause is not known. Noise-induced hearing loss produces a similar high-frequency hearing loss. Elderly patients with a high-frequency hearing loss usually have the most difficulty with appreciating consonant sounds.
- Causes of conductive hearing loss include cerumen impaction, perforation of the tympanic membrane, cholesteatoma, Paget's disease, and otosclerosis.

Treatment

- Hearing aids may be beneficial.
- Treatment of underlying cause.

Syncope

- Syncope is defined as a transient loss of consciousness with loss of postural tone. It becomes more common with advancing age and has many causes. Several serious consequences can result from the fall, including bone fracture and subdural hematoma.

Causes

- Cardiac diseases such as arrhythmias.
- Orthostatic hypotension due to peripheral neuropathy, Parkinson's disease, Shy-Drager syndrome, medications (antihypertensive agents, tricyclic antidepressants, neuroleptics, and diuretics).
- Reflex syncope due to micturition, defecation, and coughing.
- Seizures, hypoxemia (pulmonary embolism or respiratory failure), hypoglycemia, and anemia.

Treatment

- Withdraw the offending drugs.
- Treat any underlying medical condition.
- Patients are adviced to avoid getting up suddenly from lying down position.

Falls

- Falls are a common cause of morbidity and mortality among the elderly.
- Falls increase in frequency with advancing age due to multiple age-related changes, including decreased strength from loss of muscle mass, decreased visual and hearing acuity, decreased proprioception, and slowed reaction time. These changes can produce an alteration of gait and decreased balance in an elderly person.
- Most falls (70%) occur at the person's home. Falls that occur in nursing homes are more likely related to medical problems.

Evaluation of Falls

- Thorough medical history.
- The physical examination should include a neurologic examination that tests gait, balance, reflexes, sensory impairment, and extremity strength. Any sensory impairment should be noted.
- Because falls may be associated with acute illnesses, patients should be assessed for infections, myocardial infarction, and gastrointestinal tract hemorrhage.
- Orthostatic hypotension, although common among the elderly, also may indicate a medication effect or hypovolemia from hemorrhage or dehydration.

Prevention and Treatment of Falls

- Potential interventions for the prevention of falls may include the following:
  - Reduction in environmental hazards—provide adequate lighting, remove obstacles from floors, eliminate slippery floors, use appropriate footwear.
  - Physical therapy—improve gait, balance, and strength.

- Assistive devices (walking stick, etc.)—improve gait and balance.
- Review of the medications—avoid drug-drug interactions and eliminate potentially offending drugs.
- Treatment of medical problems that may contribute to falls (cataracts, postural hypotension, postprandial hypotension, Parkinson's disease).

Osteoarthritis

- Osteoarthritis is extremely common among the elderly and is present to some degree in more than 80%. It produces joint symptoms that vary with time and degree of activity
- Marked joint inflammation in osteoarthritis is uncommon.
- Radiographic findings in osteoarthritis include asymmetrical narrowing of the joint space, osteophytes, subchondral sclerosis, and cystic bone changes.

Treatment

- Adequate rest, local heat, and exercise to strengthen periarticular muscles, occasionally the injection of corticosteroids into the joint space when inflammation is present, and analgesics.

Thyroid Disease

- Most elderly patients with hyperthyroidism present with the typical findings, although they may develop apathy, depression, tremor, and myopathy. The commonest cause of hyperthyroidism in the elderly is Graves' disease.
- Symptoms of hypothyroidism are vague and often attributed to symptoms of aging. The commonest cause of hypothyroidism in the elderly is Hashimoto's thyroiditis.

Treatment

- Hypothyroidism is treated by thyroxine supplementation. Thyroxine is started at a low dose (25–50 μg daily) and gradually increased.
- Hyperthyroidism is treated by radioiodine.

Constipation

- Constipation is a common complaint in elderly. It is multifactorial.

Causes

- Decreased physical activity.
- Significant reduction in small intestinal surface area and colonic function.
- Diabetes mellitus.
- Hypothyroidism.
- Autonomic neuropathy.
- Parkinson's disease.
- Anal fissures, strictures, and hemorrhoids.
- Obstructive colonic mass lesions.

Treatment

- Increasing fluid and dietary fiber intake.
- Increasing physical activity.
- Laxatives increase stool frequency and improve symptoms of constipation.

Sexual Dysfunction

- Multiple physical and social changes occur with aging which reduce the desire and capacity of an older person for sexual activity.
- Although interest in sexuality is retained into older age, the frequency of sexual activity tends to be reduced with aging.
- In females, lack of estrogen can produce reduced vaginal lubrication and mucosal atrophy, which can cause dyspareunia.
- Erectile dysfunction increases in frequency with advancing age and is the most common reason for a man to reduce his degree of sexual activity.
- *Causes of erectile dysfunction*: Decreased libido (hypogonadism, depression), medications (antihypertensive agents, phenothiazines, antidepressants, etc.), diabetes mellitus, peripheral neuropathy, peripheral arterial disease, hypertension, thyroid disease (both hypothyroidism and hyperthyroidism), and uremia.

Treatment

- Vacuum devices.
- Intracorporeal injection of prostaglandin E1.
- Sildenafil, vardenafil and tadalafil inhibit the breakdown of cyclic guanosine monophosphate and improve blood flow to the penis.

Dementia

- Dementia is an acquired cognitive impairment that affects all spheres of the intellect. It is a gradually progressive disorder and becomes more common with increasing age.
- Prevalence 10% in those older than 65 and can be as high as 50% among those older than 90 years.
- Common causes of dementia include Alzheimer's disease (50%–70% of cases), vascular dementia (15%–25%), Parkinson disease, depression, drugs (anticholinergics, benzodiazepines), hypothyroidism, nutritional deficiencies (vitamin B_{12}, niacin, thiamine), normal-pressure hydrocephalus, and subdural hematoma.

- Driving safety is often impaired in persons with dementia.
- Screening mental status examinations often identify patients who may not have obvious cognitive impairment. The diagnosis is made primarily on the basis of the history, usually from family members, and a determination of the cognitive status of the patient.

Treatment

- Acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine) may transiently delay cognitive decline.
- Memantine is a new and novel treatment for Alzheimer's disease. It is neuroprotective and considered a disease-modifying agent. It can slow the progression of cognitive decline. This drug blocks the effect of glutamate, an excitatory neurotransmitter in CNS neurons. Glutamate stimulates N-methyl-D-aspartate receptors, which are commonly involved in memory and learning. Excessive receptor stimulation can result in damage to the receptor. Memantine inhibits the activity of glutamate, protecting the N-methyl-D-aspartate receptors from damage.
- Patients with Alzheimer's disease can be given a combination of an anticholinesterase medication and memantine.
- Evidence suggests that vitamin E and selegiline also may slow the progression of Alzheimer's disease through their antioxidant activity.

Osteoporosis

- Osteoporosis and its complications are extremely common among the elderly.
- Osteoporosis results in loss of bone density, with preservation of a normal bone-to-mineral ratio. Hip, wrist, and vertebral compression fractures are common causes of morbidity and mortality among elderly.
- The diagnosis of osteoporosis is usually made clinically.
- Bone density can be measured with several techniques, the most common of which is dual X-ray absorptiometry.

Treatment

- Initial treatment of osteoporosis in postmenopausal women should be adequate calcium intake, weight-bearing exercise, adequate vitamin D (600–800 IU/d).
- Bisphosphonates (alendronate and risedronate).
- Calcitonin.
- Raloxifene is a selective estrogen receptor modulator that reduces bone resorption and produces a modest increase in bone mineral density in the hip and spine.
- Teriparatide may be an option for a select group of patients with osteoporosis.

Urinary Incontinence

- Urinary incontinence is common among the elderly. It is much more common in females than in males. It causes numerous medical, social, and economic complications and is a common reason for nursing home placement.
- The complications include UTI, skin breakdown, social isolation, and depression.
- Three main types of incontinence are urge incontinence, stress incontinence, and overflow incontinence.
- *Urge incontinence* is due to detrusor overactivity and presents as urgency, frequency, and nocturia.
- *Stress incontinence* is due to urinary outlet incompetence from intrinsic urethral sphincter insufficiency or hypermobility the bladder. It presents as loss of small amounts of urine associated with transient increases of intra-abdominal pressure (e.g. cough, sneeze, laugh).
- *Overflow incontinence* is due to urinary outlet obstruction or detrusor underactivity. It presents as difficulty emptying bladder, low urine flow, straining to void urinary dribbling.

Evaluation of Incontinence

- Thorough medical history: Should include the amount of urine lost, duration of symptoms, precipitating factors, whether symptoms of obstruction present, and the patient's functional status.
- Symptoms of neurologic disease, associated disease states, menstrual status and parity, and medications taken should be documented.
- Physical examination to look for bladder distension and abdominal masses.
- Examination of the pelvis should include assessment for uterine, bladder, or rectal prolapse; atrophic vaginitis; and pelvic masses. The rectal examination should document any masses, fecal impaction, sphincter tone, and prostate enlargement or nodules.
- Neurologic examination to search for disease of the brain or spinal cord, autonomic nerves, or peripheral nerves.

Investigations

- Urinalysis and urine culture to check for infection, pyuria, and hematuria
- Blood urea and creatinine
- Calcium and glucose
- Intravenous pyelography or renal ultrasonography to check for hydronephrosis, postvoid residual bladder volume
- Urodynamic studies

Treatment

Urge Incontinence

- *Behavioral*: Urge suppression, elimination of bladder irritants, timed voiding.
- Antimuscarinic medications (oxybutynin, tolterodine, trospium, darifenacin, folifenacin).

Stress Incontinence

- Continence tampons, continence pessaries, pelvic floor exercises.
- *Surgical*: Urethral sling, tension-free vaginal tape, bladder suspension, injection of periurethral bulking agents, artificial urinary sphincter.

Overflow Incontinence

- Relief of bladder outlet obstruction (TURP), α-adrenergic antagonists (prazosin, terazosin), indwelling or intermittent bladder catheterization.

Diseases of the Skin

16

Q. Enumerate and define the terms used to describe skin lesions.

- *Primary skin lesions*: Primary lesions are those that occur *de novo* on a normal skin.
- *Secondary skin lesions*: These occur on pre-existing primary lesions and modify them or follow as a consequence of the primary lesions.

Table 16.1 Primary skin lesions

Term	Description	Examples
Macule	A small flat area of altered color <2 cm in diameter	Tinea versicolor, measles
Patch	Flat area of altered color >2 cm in diameter. This differs from a macule only in size	
Papule	Solid lesions raised above the surface of the skin, generally <1 cm in size. Larger papules are called nodules	Acne, warts
Plaque	A large (>1 cm), flat-topped, raised lesion	Psoriasis
Vesicle	A small, fluid-filled lesion, <0.5 cm in diameter, raised above the surface of skin. Fluid is often visible, and the lesions are translucent	Herpes simplex, chickenpox
Pustule	Similar to vesicle but filled with pus	Folliculitis
Bulla	A fluid-filled, raised, often translucent lesion >0.5 cm in diameter	Impetigo, pemphigus, pemphigoid, toxic epidermal necrolysis
Wheal	A raised, erythematous, edematous papule or plaque, usually due to short-lived vasodilatation and vasopermeability	Urticaria
Telangiectasia	A dilated, superficial blood vessel	Rosacea
Petechiae, purpura and ecchymosis	Petechiae are small pinhead-sized hemorrhages in the dermis and are not palpable. Purpura are similar to petechiae, but larger (1–3 mm) and may be palpable. Ecchymosis ('bruise') is bleeding into deeper structures	Thrombocytopenia

Table 16.2 Secondary skin lesions

Lichenification	Thickening of the skin characterized by accentuated skin-fold markings.
Scale	Excessive accumulation of stratum corneum.
Crust	Dried exudate of body fluids that may be yellow (serous crust) or red (hemorrhagic crust).
Erosion	Loss of epidermis without an associated loss of dermis.
Ulcer	Loss of epidermis and at least a portion of the underlying dermis.
Excoriation	Linear, angular erosions caused by scratching.
Atrophy	Loss of substance due to diminution of the epidermis, dermis or subcutaneous fat.
Scar	Replacement of normal structure by fibrous tissue.

Q. Discuss the etiology, clinical features, diagnosis and management of scabies.

Q. Norwegian or crusted scabies.

- Scabies is due to infestation of the skin by the mite Sarcoptes scabiei resulting in an intensely pruritic eruption.
- Crowded conditions increase the prevalence of scabies in the population.

Transmission

- It spreads from person to person by direct contact.
- It also spreads by wearing or handling contaminated clothing, or by sleeping in an unchanged bed recently occupied by an infested individual.

Etiologic Agent

- Sarcoptes scabiei, is a whitish-brown eight-legged mite which looks like a turtle. Its small size (0.4×0.3 mm) and burrowing habits prevent it from being observed by patients.
- The female mite burrows into the epidermis, lays eggs and dies in place after one to two months. Larvae hatch, leave the burrow for the surface, copulate, and continue the cycle.

Clinical Features

- The prominent clinical feature is itching. It is worse at night. Itching is due to delayed type IV hypersensitivity reaction to the mite, mite feces, and mite eggs.
- Small, erythematous papules, often excoriated may be seen. Miniature wheals, vesicles, pustules, and rarely bullae may also be present.
- The pathognomonic sign of scabies is burrow. It appears as a thin, grayish, reddish, or brownish line 2 to 15 mm long. Burrows may be absent or obscured by excoriation or secondary infection.
- The distribution of scabies usually involves web spaces of fingers, flexor aspects of the wrists, axillae. waist, genitalia, knees, buttocks and adjacent thighs. Head is spared except in very young children. In young children involvement of the palms, soles and head is common.
- Secondary infection with Staphylococcus or Streptococcus can occur.

Crusted or Norwegian Scabies

- Norwegian scabies (so-called because it was first described in Norwegian patients with leprosy) occurs in AIDS, leprosy, lymphoma, and other conditions where cellular immunity is compromised. Normally, cellular immunity prevents multiplication of scabies mites and when it is reduced, there can be unrestricted multiplication of mites. It may also be seen in patients with Down syndrome.
- Norwegian scabies begins as erythematous patches which quickly develop a prominent scale. Any area may be affected, but the scalp, hands, and feet are prominently involved. If untreated, it spreads extensively and may involve the entire body. Scales and crusts appear. The lesions are malodorous. Crusts and scales contain hundreds of thousands of mites. Nails may be discolored and dystrophic. Itching may be minimal or absent.

Diagnosis

- Diagnosis can be made from history and the distribution of lesions.
- Other members of the family are also affected.
- Presence of burrows.
- Diagnosis is confirmed by finding the mite or eggs on microscopic examination of scrapings from burrows or papules.

Treatment

Eradication of Mites

- *Topical agents*—permethrin cream (5%) is commonly used and is safe even in infants. Permethrin is applied to the entire body including head in infants and washed after 8 hours. A repeat application is required after 1 week. Other topical agents are benzyl benzoate, crotamiton, lindane, malathion, and sulfur in petrolatum.
- *Ivermectin*—this is an oral anthelmintic. A single dose of ivermectin 200 μg/kg with a repeat dose two weeks later is as effective as permethrin cream. This is very easy to administer and compliance is very good compared to topical agents. However, it is not recommended in pregnant or lactating women and safety has not been established in children with less than 15 kg weight.
- For Norwegian scabies, two doses of ivermectin two weeks apart should be given along with topical permethrin at the same time. Permethrin should be continued weekly until all scales and crusts are gone.

Control of Itching

- Antihistamines, such as diphenhydramine or cetirizine can be used. Severe itching can be controlled by topical or oral steroids.

Secondary Infection

- This is treated with appropriate systemic antibiotics.

Control of Transmission

- All family members should be treated at the same time to avoid reinfestation.

- Clothing and linen should be bagged for several days, machine washed, and then dried in a hot dryer to kill mites.
- Patients with Norwegian scabies should be isolated and treated.

Q. What are the common dermatophytoses? How do you diagnose and treat them?

- Dermatophytoses, also known as ringworm or tinea, are superficial fungal skin infections caused by dermatophytes.
- Dermatophytes belong to three genera: Microsporum, trichophyton, and epidermophyton. They can originate from the soil (geophilic), animals (zoophilic), or be confined to human skin (anthropophilic).
- These infections differ from candidiasis in that they are rarely if ever invasive.

Types

- Depending on the site of infection, dermatophytoses are classified as follows:
  - *Tinea corporis*—involvement of the body. Waist is a common site especially in obese women. Lesions are erythematous, annular and scaly, with a well-defined edge and often central clearing. They may be single or multiple and are usually asymmetrical.
  - *Tinea capitis*—involvement of the scalp and associated hair. There may be alopecia of the area involved. A soft, boggy mass with loose, easily detachable hairs may be seen (kerion). Tinea capitis is common in children.
  - *Tinea barbae*—involvement of the beard and moustache area. It presents with perifollicular pustules, erythema, crusting, seropurulent discharge and local loss of hairs.
  - *Tinea cruris*—involvement of the groins. Features are similar to those of tinea corporis.
  - *Tinea pedis (athlete's foot)*—involvement of the foot, usually interdigital spaces. It usually presents with fissuring, scaling or maceration in the interdigital areas or as scaly areas all over the soles.
  - *Tinea unguium (onychomycosis)*—involvement of nails. It presents as white discolored nails and chalky crumbling nails. There may be subungual hyperkeratosis and partial separation of nail plate. Risk factors for onychomycosis are diabetes mellitus, nail trauma, occlusive foot wear, and immunosupression.

Clinical Features

- Distribution and morphology of lesions is as described above. Lesions are scaly, have slightly raised border with central clearing.
- Patients complain of itching in the lesions which is often worse at night.
- Secondary bacterial infection of the skin lesion may occur producing pustules.

Diagnosis

- Based on history and clinical findings.
- Potassium hydroxide (KOH—10%) mount of skin scrapings—fungi are seen as long, branched and septate hyphae.
- Skin or nail biopsy
- *Culture*—on Sabouraud's medium.
- *Wood's lamp examination*—lesions of tinea versicolor and certain types of tinea capitis fluoresce when examined under Wood's lamp, emitting ultraviolet rays.

Treatment

- Topical preparations of clotrimazole, miconazole, terbinafine or ketoconazole can be applied twice daily for 4 weeks. Topical therapy is not effective for nail infections.
- For tinea capitis and barbae, ketoconazole shampoo can be used as additional therapy.
- For severe and unresponsive lesions. Oral antifungal agents can be used. These are griseofulvin, ketoconazole, fluconazole, itraconazole and terbinafine. Duration of therapy is 4–8 weeks. For tinea unguam, duration of therapy is 3 months.

Q. Tinea versicolor (pityriasis versicolor).

- This is an opportunistic fungal infection caused by *Pityrosporon orbiculare* (*Malassezia furfur*), which affects mainly the stratum corneum.

Clinical Features

- Lesions are discrete hypo- or hyperpigmented oval macules with fine scaling. Versicolor refers to the variety of colors of lesions.
- Lesions are most common on the upper trunk and extremities, and less common on the face. Seborrheic areas are the sites of predilection as sebum facilitates proliferation of *P. orbiculare*. Lesions may coalesce to form large patches.
- Most patients are asymptomatic, but some may complain of mild pruritus. It is mildly contagious, and other family members may be affected.

Diagnosis

- Diagnosis can be confirmed by examination of scrapings from lesions with 10% potassium hydroxide (KOH). Both hyphae and budding cells are seen in a pattern described as "spaghetti and meatballs".

- Wood's light examination reveals golden-white fluorescence.

Treatment

- Topical preparations of clotrimazole, miconazole, terbinafine or ketoconazole are effective.
- Selenium sulphide shampoo applied thrice weekly 10–30 minutes before bath for about 15 applications or ketoconazole 2% shampoo once daily for three days is also effective.
- Oral therapy is more convenient for patients with extensive disease. Two convenient regimens are a single 400 mg dose of ketoconazole or fluconazole 150 mg/week for 2 to 4 weeks.

Q. Enumerate various types of dermatitis (eczema). Discuss the clinical features and management of dermatitis.

- Dermatitis is superficial inflammation of the skin induced by external or internal factors. The terms 'eczema' and 'dermatitis' are synonymous.

General Features of Dermatitis

- Redness and swelling.
- Itching.
- Papules, vesicles, and rarely, large blisters.
- Oozing and crusting.
- Fissures and scratch marks.
- Pigmentation changes (hypo and hyper).
- Scaling.
- Lichenification, secondary to rubbing and scratching.

Classification and Types of Dermatitis

Exogenous	Endogenous
Irritant contact dermatitis	Atopic AA
Allergic contact dermatitis	Seborrheic DD
Photoallergic dermatitis	Discoid eczema
	Dyshydrotic (pompholyx)
	Asteatotic eczema
	Gravitational (stasis) dermatitis

- *Irritant contact dermatitis*—this occurs due to contact of skin with irritants. Dermatitis is due to direct damage caused by non-immune mechanisms as opposed to allergic contact dermatitis. Examples of irritants are cleansers, soaps, detergents, organic solvents, alkalies, and vegetables like chillies.
- *Allergic contact dermatitis*—this occurs due to delayed hypersensitivity reaction mediated by T-lymphocytes against certain chemicals (allergens) on coming in contact with the skin. Most contact allergens are haptens (incomplete allergens) which become complete allergens after combining with epidermal proteins. Examples are hair dye, shampoos, cement, etc.
- *Photoallergic dermatitis*—this occurs when the skin is exposed to sunlight following application of the chemicals to the skin of a sensitized person.
- *Atopic dermatitis*—this is due to genetic predisposition to form excessive IgE antibodies to antigens. There may be family history of atopy. Clinical features include a low threshold for itching, skin lichenification and raised serum IgE levels. In infants, the lesions are distributed on the face, scalp and front of the knees and legs. In children and adults, lesions are mainly in the cubital and popliteal fossae, sides of the neck, wrists and ankles.
- *Seborrheic dermatitis*—this is a chronic dermatitis characterized by greasy scales overlying erythematous patches or plaques. It mainly involves areas rich in sebaceous glands such as scalp, retroauricular and nasolabial folds, eyelids, trunks and axillae. It is probable due to overgrowth of *Malassezia furfur* or its yeast form *Pityrosporon ovale*, which is normally present on the skin. The disorder is more common in AIDS due to increased susceptibility to yeast infections.
- *Discoid (nummular eczema)*—this is characterized by pruritic circular or oval lesions with closely set papulovesicles on an erythematous base. It is seen most often on the limbs of elderly males.
- *Dyshydrotic eczema (pompholyx)*—this is a type of vesicular eczema with chronic and recurrent lesions affecting palms, soles and sides of the fingers.
- *Asteatotic eczema*—this is seen in hospitalized elderly, often in the lower limbs. Dry skin, low humidity, overwashing and diuretics are contributory factors.
- *Gravitational (stasis) dermatitis*—this is seen in the lower limbs due to venous insufficiency.

Investigation of Dermatitis

- *Patch tests*—useful in suspected cases of allergic contact dermatitis.
- *IgE levels* are useful in atopic dermatitis.
- Bacterial and viral swabs for microscopy and culture in suspected secondary infection.

General Management of Dermatitis

- Explanation and reassurance.
- Avoidance of contact with irritants.
- Avoidance of dryness by regular use of emollients.
- Topical corticosteroids.
- Seborrheic eczema is treated with antipityrosporal agents such as ketoconazole shampoo and creams, supplemented with weak corticosteroids.

Q. Contact dermatitis.

- Contact dermatitis (CD) is acute inflammation of the skin caused by irritants (irritant contact dermatitis) or allergens (allergic contact dermatitis).

Etiology

- Irritant contact dermatitis (ICD) accounts for 80% of all cases of contact dermatitis. It is caused by agents which directly cause irritation and inflammation of the skin. Immune system is not involved here. Agents include:
  - Chemicals (e.g. acids, alkalis, solvents, metal salts)
  - Soaps (e.g. abrasives, detergents)
  - Plants (e.g. parthenium, peppers)
  - Body fluids (e.g. urine, saliva)
- Allergic contact dermatitis (ACD) is a type IV cell-mediated hypersensitivity reaction to antigens. Some of the antigens triggering ACD are ragweed pollen, hair dye, cosmetics, poison ivy, latex rubber, etc.

Clinical Features

- ICD is more painful than pruritic. Skin changes include erythema, crusting, erosion, pustules, bullae, and edema.
- In ACD, the primary symptom is intense pruritus. Skin changes are same as those of ICD. Skin changes often occur at the site of contact with allergen, but later may spread due to scratching. Hands are commonly involved due to handling of allergens.

Diagnosis

- Clinical history and examination.
- Sometimes patch testing. Here, standard contact allergens are applied to the upper back using adhesive-mounted patches containing minute amounts of allergens.

Treatment

- Avoidance of allergens.
- *Symptomatic treatment*: Dressings for excoriation and ulceration, antihistamines for itching.
- Topical corticosteroids.

Q. Discuss the etiology, clinical features and management of psoriasis.

- Psoriasis is a chronic inflammatory disease of the skin, characterized by well-defined erythematous plaques with silvery scale.
- It is more common in European community and less common in African and Asian communities.
- It affects men and women equally. Although psoriasis can begin at any age, there seem to be two peaks in onset: One between ages 20 and 30 and another between 50 and 60.

bimodal age → : 20-30, 50-60

Etiology

→ genes → "B17"
"AD"; Autoimmune

- Psoriasis is considered to be an autoimmune disease with a genetic basis. It has a strong genetic predilection in the form of polygenic autosomal dominant inheritance with variable penetrance. Certain genes and HLA antigens (Cw6, B13, B17) are is implicated in psoriasis.
- Precipitating and aggravating factors include hormonal changes of puberty and pregnancy; infections, physical trauma (including sunlight), obesity, smoking, alcohol consumption and mental stress. Drugs like beta blockers, antimalarials, NSAIDs, lithium, etc. are known to cause psoriasiform drug reactions and also to precipitate the disease. BB Li+3
- Patients with HIV and AIDS can have severe and resistant disease at a young age.

Pathology

- There are two main abnormalities noted in psoriatic plaques:
  - Inflammatory cell infiltrate in the skin. → "erythema"
  - Hyper-proliferation of keratinocytes with a grossly increased mitotic index. "plaques"

Clinical Features

- Psoriasis is characterized by well demarcated plaques, which may vary from few millimeters to several centimeters in diameter. The lesions are red, with a "silvery-white scale."
- Extensor aspects such as elbows, knees and lower back are commonly affected. Other sites of predilection include scalp, nails, flexures and palms.
- Nails may show pitting, onycholysis (separation of the nail from the nail bed), and subungual hyperkeratosis.
- Some patients may have seronegative arthritis (psoriatic arthropathy) involving spine and/or peripheral joints.

* arthritis (sero-ve) — pso. arthropathy

Investigations

- Diagnosis is made clinically.
- Rarely skin biopsy or scraping may be required to rule out other disorders.
- X-rays and MRI may be needed if there is arthritis.

Management

- Explanation and reassurance.

Topical Therapy

- *Anthralin* is a topical antiproliferative, anti-inflammatory agent. It can cause burning sensation of skin with pain and erythema. It can also cause brown staining of the skin.

- *Coal tar*—coal tar has anti-mitotic effects and is effective in the treatment of psoriasis. Coal tar bath followed by exposure to ultraviolet light is the method commonly used. Staining of clothes and development of allergic and irritant dermatitis are its side effects.
- *Calcipotriene*—this is a vitamin D agonist. It has cytostatic and cytotoxic effects on proliferating keratinocytes. It also suppresses the underlying inflammation. It reduces the thickness and scaling of the psoriatic plaque, but does not clear the plaque. It is applied once or twice daily. Calcipotriene has almost replaced anthralin and coal tar for topical therapy.

Vit D agnst

- *Corticosteroids* are useful for many sites, particularly the flexures where tar and dithranol may be too irritant. Main side effects are local skin atrophy. Psoriasis tends to return when steroids are stopped.

PUVA Therapy

"Psoralen"

- Psoralen along with ultraviolet A (PUVA) is very effective for treatment of psoriasis. Psoralens are natural photosensitizers found in plants. Psoralen is given orally and is distributed all over the body. It gets activated only in those sites that are exposed to UVA. PUVA is as effective as intensive dithranol therapy. It is given 2 and 5 times a week and clearance occurs in the majority within 8 weeks. Main concern is increased risk of skin cancers.

-5/wk ↓ 8 weeks

Systemic Therapy

- *Methotrexate* is highly effective for psoriasis and acts by suppressing the immune system. Main side effects are bone marrow suppression, hepatic fibrosis and cirrhosis. Monitoring blood count and LFT is essential.

"MTX"

- *Oral retinoids* such as acitretin, etretinate are also effective in some patients with psoriasis. Retinoids are teratogens, hence pregnancy should be avoided for at least 2 years following their use.
- *Cyclosporin* is an immunosuppressant. It is effective in inducing and maintaining clearance of psoriasis. Side-effects include hypertension, renal impairment and immunosuppression.
- Biological agents such as infliximab, etanercept, efaluzimab have varying degrees of activity against psoriasis. They are expensive and may be considered when other treatment agents have failed.

Q. Lichen planus.

- Lichen planus is a self-limiting, itchy eruption characterized by the presence of flat-topped, polygonal papules with a violaceous hue involving the skin and mucous membranes.

Etiology

Gold

- It is an immune-mediated reaction of the skin due to diverse causes such as drugs (gold, heavy metals, sulphonamides, penicillamine), sunlight, psychological trauma and infection (hepatitis B and C).

* HBV
* HCV

Clinical Features

- Lichen planus typically affects the skin, mucous membranes, and nails. Flexor aspects of limbs, especially the wrists, are common sites of involvement.
- Lesions are flat-topped, polygonal papules with a violaceous hue. Some of them have a characteristic fine white network on their surface (Wickham's striae). New lesions may appear at the site of trauma (Köebner phenomenon).
- Nail changes range from longitudinal grooving to destruction of the nail fold and bed.
- The eruption usually lasts about 1 year. Healing may leave behind post-inflammatory pigmentation.

Diagnosis

- Clinical features.
- Biopsy of the lesion.

Management

- Usually self-limiting.
- Local corticosteroids may help in intense itching.
- Systemic corticosteroids, cyclosporin, retinoids or phototherapy may be required in severe cases.

Q. Pityriasis rosea.

- Pityriasis rosea is a self-limited, inflammatory disease characterized by diffuse, scaling papules or plaques.
- The cause may be viral infection (human herpesviruses 6, 7, and 8). Drugs may cause a similar eruption.

Clinical Features

- Affects mainly children and young adults. It affects women more often.
- Characterized by sudden appearance of oval, papulosquamous, pink or salmon colored lesions on the trunk and proximal limbs. The eruption usually begins with a "herald" or "mother" patch, a single oval pink or salmon-colored lesion on the chest, neck, or back. It is 2 to 5 cm in diameter with cigarette paper-like scales at the edges.
- A few days or weeks later oval lesions similar to the herald patch, but smaller, appear on the trunk and proximal areas of the limbs. The long axes of these oval lesions tend to be arranged along the cleavage lines of the skin. This arrangement of lesions on the back parallel to ribs gives rise to "Christmas tree pattern".

- Mild to moderate pruritus may be present.
- The rash subsides within 6–8 weeks without significant consequences.
- Differential diagnosis includes secondary syphilis, psoriasis, lichen planus and drug reactions.

Treatment

- Generally requires no treatment.
- Topical or oral steroids and antihistamines may be required to relieve itching.
- Ultraviolet light B (UVB) is helpful to reduce post-inflammatory hypopigmentation.
- Erythromycin has shown benefit in some trials. Benefit is probably due to its anti-inflammatory and immune modulating effects.

Q. What is pemphigus? Write briefly about pemphigus vulgaris.

Q. Nikolsky's sign.

- Pemphigus is a group of rare, chronic, autoimmune blistering disease affecting skin and mucous membranes (Greek pemphix = bubble).
- There are three major types of pemphigus:
  - Pemphigus vulgaris.
  - Pemphigus foliaceus.
  - Paraneoplastic pemphigus.

Etiology

- It is an autoimmune disease characterized by the presence of IgG antibodies directed against desmoglein an adhesion molecule on the surface of keratinocytes. Blister formation occurs in the epidermis due to loss of cohesion between epidermal cells, a process known as acantholysis.
- It can also occur due to drugs such as penicillins, sulphonamides, captopril, piroxicam, and antiepileptics.

Clinical Features

Pemphigus Vulgaris

- Most common form of pemphigus ("vulgar" means "common").
- Blisters are flaccid, nonpruritic, and easily break down, leaving behind erosions. Any area of the skin can be affected.
- Mucous membrane of oral cavity is commonly involved. Blisters are often found in areas subjected to friction such as cheek mucosa, tongue, palate and lower lip. Pharynx and larynx may be affected leading to pain on eating, and hoarseness of voice.

Pemphigus Foliaceous

- Blisters are more superficial than pemphigus vulgaris, which easily rupture. Hence, erosions, rather than blisters, are the presenting feature.
- Lesions first appear on the face and scalp and later on the chest and back.
- There may be associated scaling, and crusting.
- Unlike pemphigus vulgaris, mucous membrane is not affected.

Paraneoplastic Pemphigus

- Associated with malignancies, such as non-Hodgkin's lymphoma, CLL, and thymoma. Both skin and mucous membrane are affected.

Diagnosis

- The characteristic sign is Nikolsky's sign. It is elicited by applying lateral pressure to normal-looking skin at the periphery of active lesions, causing a shearing away of the epidermis leading to formation of new blisters.
- *Biopsy of skin lesions* shows intraepithelial acantholysis without disruption of the basement membrane. Direct immunofluorescence shows deposits of IgG between epidermal cells.

Differential Diagnosis

- In case of predominant mucous membrane lesions, herpes simplex, aphthous ulcers, lichen planus, and erythema multiforme have to be ruled out. In case of widespread erosions, pyoderma, impetigo, bullous pemphigoid, and bullous drug eruptions should be ruled out.

Treatment

- Without treatment pemphigus has high morbidity and mortality.
- High-dose systemic corticosteroids (e.g. prednisone 1 mg/kg/day) are the mainstay of therapy. Mild pemphigus may be treated with local steroids.
- Azathioprine and cyclosphosphamide are used as additional immunosuppressive agents. They reduce steroid requirement, decrease steroid side-effects and improve remission rate.
- Rituximab, alone or in combination with intravenous immunoglobulin (IVIG), is the treatment of choice in severe pemphigus refractory to above therapies.
- Silver sulphadiazine may be used to prevent secondary infection.

Q. Bullous pemphigoid or pemphigoid.

- Bullous pemphigoid is a subepidermal blistering disease usually seen in the elderly (>60 years of age). It is less aggressive than pemphigus vulgaris and usually not life-threatening.

Etiology

- It is an autoimmune disease characterized by linear deposits of IgG at the epidermal basement membrane. The antibodies are directed against hemidesmosomes which attach epithelial cells to the basement membrane). Hence, there is a split between the epidermis and dermis. (Note that in pemphigus the split is within the epidermis.)
- Drug-induced bullous pemphigoid develops due to penicillamine, furosemide, captopril, and antibiotics such as penicillin and nalidixic acid.
- It can be associated with systemic malignancies.

Clinical Features

- Blisters are large and tense, arising on a normal or erythematous skin. They occur anywhere on the body but common in flexural areas, groin, and axillae.
- Mucous membranes are not involved.
- Blisters are associated with marked itching. They may contain hemorrhagic fluid.
- Nikolsky's sign is negative.
- Blisters heal without scarring.
- Some patients go into spontaneous remission.

Diagnosis

- Direct immunofluorescence shows linear deposits of IgG and complement at the epidermal basement membrane.

Treatment

- Systemic steroids (e.g. prednisolone, 1 mg/kg per day).
- Azathioprine or cyclophosphamide can be used as additional immunosuppressive and steroid sparing agents.

Q. Discuss the causes, clinical features, investigations and management of Stevens-Johnson syndrome.

Or

Q. Toxic epidermal necrolysis.

- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, idiosyncratic reactions, characterized by fever and mucocutaneous lesions that culminate in epidermal necrosis and sloughing.
- SJS and TEN are similar except for the amount of area involved. Involvement of <10% of body surface area is called SJS and >30% of body surface area is called TEN; involvement of 15 to 30% of body surface area is considered SJS/TEN overlap.

Causes

Drugs

- *Anti-gout agents*: Allopurinol
- *Antibiotics*: Sulfonamides (cotrimoxazole, sulfasalazine), penicillins, cephalosporins, fluoroquinolones.
- *Antipsychotics and anti-epileptics*: Carbamazepine, phenytoin, valproate, lamotrigine, and phenobarbital.
- *NSAIDs*: Ibuprofen, piroxicam

Infections

- Mycoplasma pneumoniae

Rare

- Vaccinations, systemic diseases, chemical exposure, herbal medicines, and foods

Clinical Features

Stevens-Johnson Syndrome

- This is less severe condition with involvement of less than 10% of the body surface.
- History of drug intake prior to the onset of rash.
- Prodrome of malaise and fever, followed by the onset of erythematous or purpuric macules and plaques.
- Lesions are symmetrically distributed, and start first on the face and thorax before spreading to other areas.
- Skin lesions progress to epidermal necrosis and sloughing.
- Target lesions may be present.
- Mucosal membranes (ocular, oral, and genital) are involved in most patients. Oral and esophageal involvement causes difficulty and pain while swallowing. Genitourinary involvement causes dysuria and difficulty to void. Bronchial epithelium may also slough, causing cough, dyspnea, pneumonia, pulmonary edema, and hypoxemia.
- Glomerulonephritis and hepatitis may develop.

Toxic Epidermal Necrolysis

- This is a more severe condition with involvement of more than 30% of the body surface area.
- Other features are same as SJS.

Investigations

- Anemia and neutropenia may be present.
- AST and ALT may be elevated.
- Skin biopsy may be required.

Differential Diagnosis

- Erythema multiforme.
- Viral exanthems.
- Drug rashes.
- Toxic shock syndrome.

- Exfoliative erythroderma (usually spares mucous membranes).
- Paraneoplastic pemphigus.

Management

- Treatment of underlying cause (e.g. withdrawal of causative agent).
- Maintenance of fluid and electrolyte balance.
- Antihistamines and local steroids are enough for mild cases.
- Silver-impregnated nanocrystalline gauze for topical wound care.
- Systemic corticosteroids are indicated in severe cases. Prednisolone, 1 to 3 mg/kg daily or an equivalent amount of other steroids can be used.
- IV immunoglobulin (1 g/kg daily for three consecutive days) is also useful in severe cases of SJS and TEN.
- Sepsis is the major cause of death. Systemic antibiotics should be given at the first sign of wound infection.

Q. Erythema multiforme.

- Erythema multiforme is an acute inflammatory skin disease characterized by target or iris skin lesions.
- Earlier, erythema multiforme major was being equated with Stevens-Johnson syndrome. But now most authorities think that these two entities are different.

Etiology

- Majority of cases are caused by herpes simplex virus (HSV) infection (HSV-1 more so than HSV-2).
- Some cases are caused by drugs (sulfonamides, NSAIDs, and anticonvulsants), vaccines, other viral diseases (especially hepatitis C), and SLE.

Clinical Features

- Classic manifestation is target lesion, consisting of three concentric zones of color change. Centre and periphery of the lesion is red and in between there is pale area. Such classic lesions are found in herpes simplex infection. They are most often found on the hands and feet. Wheals, vesicles, and bullae can also be seen.

Differential Diagnosis

- Urticaria.
- Drug eruptions.
- Paraneoplastic pemphigus.

Treatment

- Withdrawal of offending agent.
- Treatment of infection.
- Systemic steroids in severe cases.

Q. Discuss the etiopathogenesis, clinical features and management of acne vulgaris.

- *Acne vulgaris* is a chronic skin condition involving blockage and/or inflammation of pilosebaceous units (hair follicles and their accompanying sebaceous gland).
- Acne is seen in most teenagers. Peak severity is in the late teenage years but acne may persist into the third decade and beyond, particularly in females.

Puberty → Androgens → Sebum↑ → block

Etiopathogenesis

- Acne occurs through the interplay of 4 major factors: Increased sebum production, follicular plugging with sebum and keratinocytes, colonization of follicles by *Propionibacterium acnes*, and release of multiple inflammatory mediators.
- Increased sebum production—with the onset of puberty, sebaceous glands enlarge and sebum production increases. There is a clear relation between severity of acne and sebum production. In the complete absence of sebum, acne does not occur. Androgens are mainly responsible for increased sebum production.
- Follicular plugging with sebum and keratinocytes: Blockage of pilosebaceous duct due to retention of keratinous material and sebum leads to formation of small cysts, called comedones.
- Colonization and activity of bacteria (*Propionibacterium acnes*) within the comedones releases free fatty acids from sebum, causes inflammation within the cyst and rupture. Sebum → FA (inflamm).
- Rupture of the cyst releases oily and keratinous debris leading to an inflammatory foreign body reaction in the skin.

Clinical Features

- The clinical hallmark of acne vulgaris is the comedone, which may be closed (whitehead) or open (blackhead).
- Closed comedones appear as 1–2 mm white papules. Open comedones have a large follicular orifice and are filled with oxidized, darkened, oily debris (black).
- Inflammatory papules, nodules and cysts occur and healing may lead to scarring.
- Lesions are maximum on the face, but may also occur on shoulders, upper chest and back.

Management

- Treatment of acne vulgaris is directed toward elimination of comedones by normalization of follicular keratinization, decreasing sebum production, decreasing the population of *P. acnes*, and decreasing inflammation.

comedones↓ → Sebum↓ Keratin↓

Local Measures

- Enough for mild to moderate acne.
- Regular washing with soap and water.
- Topical keratolytic agents—retinoic acid, benzoyl peroxide, or salicylic acid. They alter the pattern of epidermal desquamation and prevent the formation of comedones.
- Topical antibacterial agents—azelaic acid, topical erythromycin, or clindamycin. They inhibit *Propionibacterium acnes*.
- Incision and drainage of cysts.
- Intralesional injection of triamcinolone acetonide reduces inflammation and hastens the resolution of cysts.
- Dermabrasion and excision of scars to improve skin appearance.

Systemic Measures

- Useful in severe acne with prominent inflammatory component.
- *Antibiotics*—tetracycline (250–500 mg bid), or doxycycline (100 mg bid). These antibiotics have anti-inflammatory effect in addition to their antibacterial effect. Oral antibiotics should be given for at least 6 months.
- Systemic retinoids (isotretinoin) are useful in severe acne unresponsive to other therapies. Retinoids have significant adverse effects including teratogenicity.
- Estrogens (oral contraceptives) also improve acne in women.

6 months

OCP's

Q. Miliaria (heat rash).

- In miliaria, blockage of sweat ducts produces skin lesions. It occurs in hot and humid weather.

Clinical Features

- Lesions are small, superficial, red, thin-walled, discrete but closely aggregated vesicles, papules, pustules or vesicopustules. Itching and burning is usually present.
- Miliaria occurs most commonly on the covered areas of skin such as trunk and intertriginous areas. In hospitalized patients, it occurs commonly on the back.

Treatment

- Patient should keep cool and wear loose and light clothing.
- Local application of triamcinolone acetonide, or a mid-potency corticosteroid in a lotion or cream base.
- Antibiotics for secondary infections (dicloxacillin).
- Anticholinergic drugs may be helpful in severe cases (glycopyrrolate, 1 mg twice daily). They help by decreasing sweating.

Q. Warts.

- Warts are mucocutaneous manifestation of human papillomavirus (HPV) infection.
- Viral warts are extremely common and most people suffer from one or more at some point during their life. HPV spreads by direct or sexual contact.

Clinical Features

- Common warts (verruca vulgaris) have smooth surface intially, but as they enlarge, their surface becomes irregular and hyperkeratotic, producing the typical warty appearance. They are most common on the hands but may also be seen on the face, genitalia, arm and leg. They are usually multiple.
- Plane warts (verruca plana) are smooth, flat-top papules seen most commonly on the face and backs of hands.
- Plantar warts (verruca plantaris) have a rough surface, surrounded by a horny collar. Plantar warts may be painful and disabling.
- Other types of wart are mosaic warts (mosaic-like plaques of tightly packed individual warts), facial warts (often filiform), and genital warts, which may be papillomatous and protuberant.

Treatment

- *Wait and watch*—spontaneous regression occurs in two-thirds of warts within two years. However, it is better to treat to avoid the risk of spread.
- Warts can be destroyed by local application of liquid nitrogen, salicylic acid, CO_2 laser, bichloroacetic acid, or cantharidin. Surgical excision and electrocautery are other options.
- Bleomycin injection into warts has a high cure rate for plantar and common warts.
- Podophyllum resin and the immunomodulator imiquimod are useful in anogenital warts.

Q. Erythema nodosum.

- Erythema nodosum (EN) is a specific form of panniculitis (inflammation of subcutaneous fat) characterized by tender, red or violet, palpable, subcutaneous nodules.
- Most likely represents a delayed hypersensitivity reaction to antigens associated with the various infectious agents, drugs, and other diseases.

Causes

- Idiopathic (most common cause)
- Streptococcal pharyngitis (most common known cause)
- Tuberculosis

(contd.)

- Leprosy
- Other infections (HIV, syphilis, systemic fungal infections, yersiniosis)
- Sarcoidosis
- Inflammatory bowel disease
- SLE
- Behçet's disease
- Hodgkin's lymphoma
- Pregnancy
- Drugs (oral contraceptives, sulfa drugs)

Clinical Features

- EN primarily affects people in their 20s and 30s but can occur at any age; women are more often affected.
- The lesions are deep nodules, 1–10 cm in diameter, red or violet in color and tender.
- They are most often located on the anterior surfaces of the legs below the knees (shin) but may rarely occur on the arms, trunk, and face.
- Fever, malaise, and arthralgia usually accompany the lesions.
- Lesions last about 6 weeks and heal without scarring
- Recurrence may occur.

Diagnosis

- Diagnosis is mainly based on clinical features.
- WBC, ESR and CRP are elevated.
- Appropriate tests to identify the underlying cause (chest X-ray, montoux test, ANA, ASO titre, etc.).
- Biopsy may be required in atypical cases.

Treatment

- Usually self-limited.
- Underlying cause should be identified and treated.
- Pain, arthralgia and fever can be treated by NSAIDs.
- Potassium iodide solution, 5–15 drops orally three times daily, results in prompt involution in many cases. Exact mechanism of action of potassium iodide is unknown.
- Oral corticosteroids in severe, extensive disease unless contraindicated by associated infection.

Q. Vitiligo.

- Vitiligo is skin depigmentation due to selective destruction of skin melanocytes.

Etiology

- In vitiligo there are focal areas of melanocyte loss which is considered to be due to cell-mediated autoimmune attack. Some patients have antibodies to melanin. It may be associated with other autoimmune diseases such as diabetes, Addison's disease and pernicious anemia.
- Genetic factors may play a role; 20 to 30% of patients may have a family history of vitiligo.
- Extrinsic factors also may play a role. Trauma, certain chemicals and sunburn may precipitate the appearance of vitiligo.

Clinical Features

- Lesions may start at any age, but generally in early adolescence or adult life.
- Segmental vitiligo is restricted to one part of the body.
- Generalized vitiligo is characterized by many widespread macules, often symmetrical and frequently involves the hands, wrists, knees and neck as well as the area around the body orifices.
- The patches of depigmentation are sharply demarcated.
- Sensation in the depigmented patches is normal unlike leprosy.
- Course is static or slowly progressive. Some patients may experience spontaneous repigmentation.

Differential Diagnosis

- Postinflammatory hypopigmentation.
- Piebaldism (a rare autosomal dominant disorder; depigmented patches surrounded by hyperpigmented areas).
- Morphea (localized scleroderma).
- Leprosy (lesions are usually hypoesthetic).
- Lichen sclerosus.
- Pityriasis alba.
- Chemical leukoderma.
- Leukoderma due to melanoma.

Management

- ***Corticosteroids***: Topical corticosteroids are the first choice for patients with limited disease. Topical preparations of fluticasone propionate or mometasone, once a day for four to six months has to be applied. Oral corticosteroids may be helpful in progressive disease.
- ***Calcineurin inhibitors***: Topical calcineurin inhibitors (e.g. tacrolimus) are also effective.
- ***Ultraviolet light***: Topical or oral psoralens plus ultraviolet A radiation (PUVA), or ultraviolet B (UVB) radiation (phototherapy) is used in patients with extensive vitiligo. A total of 75 to 150 treatments (e.g. three times/week for 6 to 12 months) may be necessary.
- ***Surgery***: Split-skin grafts and blister roof grafts, can be used to cover vitiligo patches.
- ***Depigmentation therapy***: If there is extensive vitiligo with only small areas of normal skin, these normal skin areas can be depigmented (by using hydroquinone) to make the skin look uniform.

- Patients should be advised to avoid excessive sun exposure and to use sunscreens to reduce the risk of skin cancer in the long run.
- Camouflage cosmetics may also be helpful to mask the patches.

Q. Keloid and hypertrophic scar.

Keloids

- Keloids (Greek word meaning "tumor-like") are benign fibrous growths present in scar tissue.
- They occur due to altered wound healing, with over-production of extracellular matrix and dermal fibroblasts that have a high mitotic rate.
- Keloids extend beyond the margins of original scar.
- They may be pruritic, tender, painful and disfiguring.
- Common locations are ears, neck, jaw, sternal area, shoulders, and upper back.
- Recurrence is common after treatment.

Hypertrophic Scars

- Hypertrophic scars appear similar to keloids, but do not extend beyond the margins of the scar and they are less likely to recur after treatment.

Treatment

- Intralesional injection of corticosteroids such as triamcinolone is the first-line therapy for most keloids. Intralesional injection of fluorouracil, interferon or verapamil is also effective.
- Surgical excision may be indicated if injection therapy alone is unsuccessful. Excision should be combined with triamcinolone or interferon injections.
- Silicone gel sheeting (applying a soft, semiocclusive dressing made of silicone) can reduce pain and itching of keloids and also reduce the size and occurrence of new keloids. The mechanism of anti-scarring effect of silicone gel is unknown.
- Other treatments used are cryosurgery, radiation therapy, laser therapy, pressure garments and topical imiquimod cream.

Q. Melanocytic nevi (moles).

- Melanocytic nevi (moles) are localized benign proliferations of melanocytes. Moles are a usual feature of most human beings. They are used as identification marks.
- They probably occur due to abnormalities of the normal migratory pattern of the melanocytes during development.

Clinical Features

Congenital Nevi

- These are present at birth or appear shortly after.

Acquired Nevi

- These appear in early childhood, at adolescence, and during pregnancy or oestrogen therapy. They can be divided into 3 types based on the location of clumps of melanocytes.
- *Junctional nevi*—these are present in the dermal-epidermal junction. They are common on the acral surfaces but may occur anywhere. They appear as flat, pigmented macules.
- *Compound nevi*—these are present in the dermo-epidermal junction as well as dermis. They are often raised, and may be papillomatous.
- *Dermal nevi*—these are present in the dermis only. They are typically flesh colored.

Significance of Moles

- Most moles are benign and do not cause any problems. Rarely there may be malignant transformation. Malignant change is most likely in large congenital melanocytic nevi.

Danger Signs Indicating Malignant Transformation of Moles

- Itching
- Increase in size
- Change in color
- Change in shape
- Bleeding
- Irregular margin or surface
- Inflammation
- Ulceration

Management

- Most nevi do not require any treatment.
- Excision may be considered if malignancy is suspected or when they repeatedly become inflamed or traumatized or for cosmetic reasons.

Q. Alopecia (baldness).

- Alopecia refers to loss of hair from the body. It is a sign rather than a diagnosis.
- Hair grows in cycles. Four stages of hair growth can be recognized; anagen, catagen, telogen and exogen. Different hairs will be at different phase at any given time.

- Anagen is long growing phase which lasts from 2 to 6 years. Catagen is a brief transitional phase where the hair follicle shrinks in size. Telogen is a short resting phase lasting 1 to 4 months. At the end of the resting phase, the hair falls out (exogen) and new hair starts growing in the follicle, beginning the cycle again.
- Alopecia can be broadly classified into scarring and non-scarring types. It can be localized or diffuse.
- Scarring alopecia refers to hair loss associated with fibrosis that replaces and often permanently destroys the hair follicle.
- Nonscarring alopecia refers to hair loss without permanent destruction of the hair follicle.

Causes of Alopecia

Scarring alopecia	Nonscarring alopecia
Herpes zoster Chemical or physical trauma Discoid lupus erythematosus Scleroderma Severe folliculitis Lichen planopilaris Dissecting cellulitis Tumors Radiotherapy Idiopathic	Androgenetic alopecia (most common cause) Tinea capitis Alopecia areata Traumatic (trichotillomania, traction) Syphilis Telogen effluvium Hypo- and hyperthyroidism Hypopituitarism Diabetes mellitus HIV Nutritional deficiency (e.g. iron) Liver disease Post-partum Drugs (anticancer drugs, antithyroid drugs, oral contraceptives, allopurinol, gentamicin, and levodopa)

Clinical Features

- Note the onset and duration of hair loss, whether hair shedding is increased, and whether hair loss is localized or diffuse. Hair loss can be local or diffuse depending on the cause. Both scalp and body hair loss is seen in alopecia universalis. Loss of up to 100 hairs per day is normal. More than this is significant.
- History of recent exposures to noxious agents (e.g. drugs, toxins, radiation) and stressors (e.g. surgery, chronic illness, fever, psychologic stressors) suggests toxic or stress induced hair loss.
- History of weight gain, fatigue and cold intolerance suggests hypothyroidism. History of virilization in women (hirsutism, deepening of the voice, and increased libido) suggests adrenal disorder or polycystic ovary syndrome. History of gynecologic/obstetric complaints in women may suggest hormonal problems.
- A family history of hair loss should be recorded.
- Alopecia areata appears as sharply demarcated bald patches, with pathognomonic 'exclamation mark' hairs (broken-off hairs 3–4 mm long, which taper off towards the scalp). The hair usually regrows in small bald patches, but may be incomplete in larger patches.
- Androgenetic alopecia or male-pattern baldness is physiological in men over 20 years old. Hair loss usually occurs in an M-shaped pattern (bitemporal recession and then crown involvement) in the frontal hair line. It also occurs in females, usually after menopause, but hair loss is often diffuse.
- Hair loss associated with pruritus, erythema, and scaling is seen in chronic cutaneous lupus and tinea capitis.
- Asymmetric, bizarre, irregular hair loss pattern is seen in trichotillomania.

Investigations

- Serum testosterone, DHEA.
- Iron, total iron binding capacity.
- Urea, creatinine, electrolytes, LFT.
- Thyroid function tests.
- ANA.
- HIV, VDRL and TPHA.
- Fungal stain in localized hair loss with scaling.
- Scalp biopsy, with direct immunofluorescence, if lichen planus or discoid lupus erythematosus is suspected.

Management

- Support and reassurance.
- Treatment of underlying cause.
- Alopecia areata sometimes responds to topical or intralesional corticosteroids such as triamcinolone.
- Systemic finasteride or topical 2% minoxidil solution are useful in severe androgenetic alopecia. In females, anti-androgen therapy such as cyproterone acetate can be used.
- Scalp reduction surgery and autologous hair transplantation are also options in irreversible alopecia.
- Wig may be useful for irreversible extensive alopecia.

Q. Discuss briefly the common skin malignancies.

Basal Cell Carcinoma (BCC) (Rodent Ulcer)

- This is the most common skin cancer. It arises from the basal layer of epidermis and its appendages.

- Both environmental and genetic factors contribute to the development of BCC. Chronic exposure to ultraviolet (UV) radiation in sunlight is the most important risk factor. Other risk factors are chronic arsenic exposure, therapeutic radiation, immunosuppression, and the basal cell nevus syndrome.
- It is common in Europeans and at least 3 times more common than squamous cell carcinoma.
- It is more common in men than in women probably due to more exposure to sun.
- Incidence increases with age.

Clinical Features

- Most BCCs occur on the face.
- Most common type is nodulo-ulcerative form. The earliest lesion is a small papule, with fine telangiectatic vessels on the surface, which slowly enlarges. Central necrosis may occur, leaving an ulcer surrounded by a rolled pearly edge.
- The tumor invades locally but rarely metastasizes.
- The superficial (multifocal) variant is seen most often on the trunk; it appears as a slowly enlarging pink or brown scaly plaque.

Management

- Since metastasis is extremely rare, most BCCs can be treated by local destruction.
- Treatment options include surgery, cryotherapy, radiotherapy, photodynamic therapy or the topical immunostimulant imiquimod. Surgery is usually the first choice, as it allows histological assessment of the tumor and examination of tumor margins.

Squamous Cell Carcinoma (SCC)

- SCC is the second most common skin cancer after BCC.
- Risk factors for SCC are similar to BCC. Additional risk factors are chronic cutaneous ulcer, genetic disorders such as dystrophic epidermolysis bullosa and xeroderma pigmentosum, human papillomavirus infection, and smoking.

Clinical Features

- SCC arises most commonly in areas frequently exposed to the sun, such as the head and neck (most common site), dorsum of the hands and forearms, and legs.
- Varying clinical presentations include nodules, plaques, infiltrating tumors and ulcers.
- Histological grade varies from well-differentiated to anaplastic. SCCs of the lip behave more aggressively and show a greater frequency of metastasis.

Management

- Surgical excision is the preferred option because of the definite risk of metastasis.
- Other options are cryotherapy, electrosurgery (i.e. curettage and electrodesiccation), topical treatment (5-fluorouracil, or imiquimod) and radiotherapy.

Malignant Melanoma

- Incidence of malignant melanoma has increased in recent decades. There is no effective treatment for metastatic melanoma and hence, the main focus is on primary prevention and early detection.
- Malignant melanoma has very poor prognosis with a case fatality rate of approximately 20–25%.
- The main risk factors for melanoma are ultraviolet rays exposure, pale skin, melanocytic nevi, immunosupression, and family history of melanoma. About 30–50% of melanomas develop in a pre-existing melanocytic nevus. Development of any danger sign in a nevus should raise the suspicion of malignant transformation.

Clinical Features

- *Superficial spreading*—this is characterized by superficial and radially expanding, pigmented macule or plaque. Its margin is usually irregular.
- *Lentigo maligna*—this is the *in situ* phase of superficial spreading melanoma. It occurs most often on the exposed skin of the elderly. Lentigo maligna may have been present for many years before invasive melanoma develops from it.
- *Nodular*—appears as a pigmented nodule.
- *Acral lentiginous*—it occurs on the palms and soles.
- In amelanotic melanomas, pigmentation is minimal or absent.
- Subungual melanomas present as painless, expanding areas of pigmentation under a nail.
- *Clinical stages of malignant melanoma*
  - Stage I—primary lesion only
  - Stage II—involvement of regional lymph nodes
  - Stage III—distant metastases (nodal or visceral)

Management

- Surgical excision is the treatment choice. Palpable local nodes in stage II patients should be removed by block dissection.
- Chemotherapy is rarely curative but can be palliative in stage III disease or earlier.
- Alpha-interferon may reduce recurrences in patients with high-risk melanomas.

Q. Skin manifestations of internal disease.

Many systemic diseases manifest as skin diseases which can serve as a clue to systemic disease. The type of lesion typically relates to a specific disease or type of disease.

- *Erythema nodosum*: TB, leprosy, syphilis, sarcoidosis, inflammatory bowel disease, SLE.
- *Acanthosis nigricans*: Internal malignancy, insulin resistance.
- *Pyoderma gangrenosum*: Inflammatory bowel disease.
- *Hyperpigmentation*: Hemochromatosis, Addison's disease, ectopic ACTH syndrome, vitamin B_{12} deficiency, pellagra.
- *Hypopigmentation*: Oculocutaneous albinism, Chèdiak-Higashi syndrome, phenylketonuria, systemic sclerosis (scleroderma), leprosy, tuberous sclerosis
- *Xanthomas and xanthelasma*: Elevated serum triglycerides.
- *Acanthosis nigricans, necrobiosis lipoidica, and scleredema*: Diabetes mellitus.
- *Thick and dry skin*: Hypothyroidism.
- *Striae and skin fragility*: Cushing's disease.
- *Skin ulcers*: Vasculitis, sickle cell anemia, cryoglobulinemia, diabetes mellitus.
- *Vesicles/bullae*: Paraneoplastic pemphigus, porphyrias
- *Purpura*: Thrombocytopenia, clotting factor defects, Ehlers-Danlos syndrome, scurvy, DIC, APLA, thrombotic thrombocytopenic purpura, cholesterol and fat emboli, systemic vasculitis, acute meningococcemia.
- *Alopecia*: SLE, secondary syphilis, hypothyroidism, hyperthyroidism, deficiencies of protein, biotin, zinc, and iron.
- *Urticaria*: Urticarial vasculitis, hepatitis B or C infection, serum sickness
- *Acneiform eruptions*: Cushing's disease, congenital adrenal hyperplasia, polycystic ovary syndrome.
- *Telangiectasias*: Carcinoid syndrome, ataxia-telangiectasia, hereditary hemorrhagic telangiectasia
- *Spider angioma*: Cirrhosis
- *Pruritus*: Occult cancer, often lymphoma.

17 Poisoning, Venomous Bites and Environmental Diseases

Q. Discuss the general management of a patient who has ingested a poison/drug overdose.

- A poison is a substance which produces adverse effects in a living organism.
- Poisoning may be accidental, intentional (suicidal) or homicidal. Accidental ingestion of poison is common in children. Overdosage of 'recreational' drugs is frequent in young adults. Intentional (suicidal) poisoning is seen in adults of all ages. Homicidal poisoning (with the intention of murdering) is less common.
- Commonly ingested poisons are organophosphorus and organochloride insecticides, vegetable poisons (oleander), aluminum phosphide, methyl and ethyl alcohol, hypnotics and sedatives. Insecticide and vegetable poisoning is common in rural areas because of easy availability. Sedative overdosage is mainly encountered in the cities and towns.

General Management of a Case of Poisoning

- Management of poisoning involves the following steps:
  - Resuscitation and initial stabilization.
  - Diagnosis of type of poison.
  - Prevention of further absorption of poison.
  - Administration of antidote.
  - Increasing the clearance of absorbed poison.
  - Prevention of recurrence of poisoning.

Resuscitation and Initial Stabilization

- Airway, breathing and circulation (A, B and C) should be attended to first, even before obtaining a history.

Airway

- Airway may be compromised by aspiration of pharyngeal secretions or vomitus, by laryngeal edema in corrosive poisoning and anaphylaxis, or stridor in strychnine poisoning. Airway can be opened by positioning, suction, or insertion of an artificial nasal or oropharyngeal airway. Endotracheal intubation is required if the patient is deeply comatose without any gag or cough reflex. Emergency tracheostomy is required if there is laryngeal obstruction.

Breathing

- Once the airway is opened by the above procedures, assess the patient for the rate and depth of breathing. Pulse oximetry can be useful to assess the adequacy of breathing, but is not reliable in methemoglobinemia or carbon monoxide poisoning. An urgent ABG (arterial blood gas analysis) provides important information about blood pH, paO_2 and pCO_2. If breathing is inadequate, it should be assisted by bag-mask device or mechanical ventilation. Supplemental oxygen should be given.

Circulation

- Next, assess the patient for adequacy of circulation by measuring pulse rate and BP. Tissue perfusion can be assessed by urinary output, skin signs, and arterial blood pH. If BP is low, a large-bore IV line should be inserted and infusion of fluids (DNS or NS) started. Bradycardia can occur in sedative and OP poison ingestion and should be corrected by atropine injection intravenously. If BP does not pick up even after infusion of fluids, inotropes such as dopamine or noradrenaline infusion should be started. Patient should be put on continuous electrocardiographic monitoring.
- Before any fluid is given, blood should be drawn for complete blood count, glucose, electrolytes, serum creatinine and liver tests, and toxicologic screening.

Diagnosis of Type of Poison

- The diagnosis and treatment of poisons must proceed rapidly without waiting for the results of toxicologic screening.
- Type of poison, quantity and time of ingestion can be obtained by history, physical examination and laboratory tests. Relatives and bystanders may be able to give useful information. They should be asked to get the container

of the suspected poison or drug. Odor or appearance of the stomach contents may help in identification of the poison. A toxicological analysis of blood can be performed if the poison cannot be identified by the above means.

Identification of Poison Based on Clinical Features

Clinical feature	Possible poison/drug
Coma	Narcotics, benzodiazepines, barbiturates, alcohol, methanol, hypoglycemia, organophosphorus
Pupil size	*Constricted*—opioid, phenothiazines, organophosphorus *Dilated*—alcohol, anticholinergics, Datura, botulism, carbon monoxide
Respiratory rate	*Reduced*—opioids, benzodiazepines *Increased*—salicylates, methanol, ethylene glycol
Blood pressure	*Hypotension*—TCAs, antihypertensives *Hypertension*—cocaine, amphetamines, sympathomimetics
Heart rate	*Bradycardia*—organophosphorus, digoxin, beta blockers, opioids. *Tachycardia*—coccaine, theophylline, anticholinergics
Body temperature	*Increased*—Datura, atropine, SSRIs *Decreased*—sedatives, opioids
Jaundice	Phosphorus, isoniazid, rifampicin, carbon tetrachloride, paracetamol
Cyanosis	*Methemoglobinemia*—aniline dyes, sulphonamides, nitrates
Cherry-colored skin and mucous membranes	Carbon monoxide
Bullous rash	Barbiturates
Dystonias, muscle spasms	Phenothiazines, metoclopramide, strychnine
Burns and ulcers in the lips and mouth	Corrosive poison

Prevention of Absorption of Poison

Emesis

- Vomiting can remove unabsorbed poison from the stomach when performed within 3–4 hours of ingestion. Patient must be fully conscious and have stable breathing and circulation. Emesis is contraindicated in corrosive and hydrocarbon (like kerosene) ingestion. Kerosene can cause fatal chemical pneumonitis if aspirated during vomiting.
- Emesis can be induced by drinking 200 to 400 ml of a fully saturated sodium chloride solution, subcutaneous apomorphine, or syrup of ipecac (10 to 30 ml). Apomorphine and syrup of ipecac act by stimulation of vomiting center.
- Emesis is less commonly used now, because of the risk of aspiration.

Gastric Lavage

- It is performed by passing a wide-bore nasogastric tube. Patient should be in lateral decubitus position with the head 15° to 20° lower than the feet (Trendelenburg position).
- Stomach contents are emptied, and then lavage is performed by introducing 200 to 300 ml fluid into the somach at a time. The fluid is allowed to drain out by gravity. Lavage is performed till the draining fluid is clear. Up to 3 to 5 liters of water may be required. Warm normal saline or tap water is used as lavage fluid to prevent hypothermia. Food particles may block the tube and prevent adequate emptying of the stomach. Intact tablets are incompletely recovered by gastric lavage.

Activated Charcoal

- Activated charcoal is fine charcoal powder which is heated with steam, air, or carbon dioxide to add more surface area.
- It has an extensive network of interconnecting pores that bind (adsorb) and trap chemicals, thereby preventing their absorption and toxicity.
- It is usually given after gastric lavage. The dose is 1 g/kg body weight (maximum 50 to 60 g) as a single dose. Multiple doses can be used in cases of poisons which undergo enterohepatic circulation. Side-effects of charcoal include nausea, vomiting, and diarrhea or constipation.

Whole Bowel Irrigation

- Whole bowel irrigation (WBI) refers to the administration of large volumes of a balanced electrolyte solution with polyethylene glycol, via a nasogastric tube, to decontaminate the GI tract without causing fluid or electrolyte shifts. 1 to 1.5 liters of solution per hour is given until the rectal effluent is clear, which usually takes four to six hours.
- WBI is particularly useful in ingestion of enteric-coated pills, sustained-release preparations, illicit drug packets, and large ingestions of substances poorly bound by charcoal, such as iron, lithium and lead.

Administration of Antidote

- Antidotes counteract the effects of poisons by neutralizing them or by antagonizing their physiologic effects. Antidotes are available only for a few poisons.

Commonly Used Antidotes

Poison/drug	Antidote
Organophosphates	Atropine, PAM
Paracetamol	N-acetylcysteine
Cyanide	Dicobalt edetate, sodium nitrate
Methanol	Fomepizole, ethanol
Amanita phalloides	Benzyl penicillin
Calcium-channel blockers	Calcium chloride
Methotrexate	Folinic acid
Anticholinergics	Physostigmine
Beta blockers	Glucagon
Benzodiazepines	Flumazenil
Warfarin-like compounds	Vitamin K
Lead, arsenic, mercury	Dimercaprol (BAL), D-penicillamine
Iron	Desferrioxamine
Opioids	Naloxone
Digitalis	Digoxin immune Fab (digibind)

Increasing the Clearance of Absorbed Poison

Alkaline Diuresis

- Alkalinization of urine enhances excretion of acidic drugs by increasing the ionic form of the drug in urine, thereby preventing its reabsorption by tubules.
- It is effective in poisoning due to salicylates, barbiturates, sulfonamides, barium, bromides, calcium, etc.

Hemodialysis and Hemoperfusion

- Dialysis is based on the property of drugs and toxins to diffuse down a concentration gradient across a semi-permeable membrane. Hemodialysis is useful in poisoning of methanol, ethylene glycol, isopropanol, salicylates, theophylline, and lithium.
- Hemoperfusion refers to the circulation of blood through an extracorporeal circuit containing an adsorbent such as activated charcoal or polystyrene resin. It is useful in poisoning due to amanita mushroom, amitriptyline, barbiturates, digitalis, methotrexate, paraquat, phenytoin and theophylline.

Prevention of Recurrence of Poisoning

- Some patients may make another suicidal attempt by consuming poison. Hence, all patients should be referred for psychiatric evaluation.

Q. Classify poisonous snakes. Discuss the clinical manifestations, diagnosis and management of snakebites.

- Snakebite is a common life-threatening condition worldwide, especially in tropical countries. Farmers, hunters and rice-pickers are at particular risk of snakebite.
- More than 5 million poisonous snakebites occur annually worldwide, with >125,000 deaths. Nearly 40% of bites by venomous snakes do not produce signs of envenomation. The peak seasonal incidence is usually during the monsoon. Most of the bites occur in the evening, after sunset, when snakes come out for feeding. Nearly 75% of snake bites occur in outdoor and in rural settings. Males are bitten twice as often as females. Most frequent site of bite are lower limbs.

Major Families of Poisonous Snakes

Family	Main toxic effect
Elapidae: Cobras, kraits, mambas, coral snakes	Neurotoxic
Hydrophidae: Sea snakes	Myotoxic
Viperidae: Vipers and pit vipers	Severe local reaction, coagulation defects, renal failure

Composition of Snake Venoms

- Snake venoms are complex mixtures of enzymes, polypeptides, glycoproteins, and metal ions. Most snake venoms have multisystem effects. Major components are as follows:
  - *Hemorrhagins*—cause vascular leakage and bleeding.
  - *Procoagulants*—activate clotting factors and cause consumptive coagulopathy.
  - *Proteolytic enzymes*—cause local tissue necrosis, coagulation defects, and organ damage.
  - *Cardiotoxins*—myocarditis, reduce cardiac output.
  - *Neurotoxins*—act at peripheral neuromuscular junctions and inhibit nerve impulses.
  - *Myotoxins*—local tissue necrosis, rhabdomyolysis.

Clinical Features of Venomous Snakebite

- Snakebite victims usually develop anxiety and fear. This may lead to hyperventilation which causes paresthesia, and carpopedal spasm. Some may develop syncope, vasovagal shock and may even collapse. Clinical presentation of snakebite varies depending on the type of snake bitten, age of the patient, the area bitten, and the amount of poison injected.

Snakebite without Envenomation

- This can happen when a person is bitten by a non-poisonous snakebite, or when a poisonous snake fails to inject poison. If a poisonous snake has bitten a prey prior

to biting a person, then the poison would have been injected into the prey and hence, there will not be poison injection into the person. Similarly when the snakebites into bony areas such as shin, or heel, there is a little venom deposited because of the absence of adequate tissue space to accommodate the poison.

Local Manifestations

- It manifests as pain, tenderness, paresthesia at local site followed by swelling of bitten limb. Entire limb with adjacent trunk can get involved. Severe local reaction leads to local tissue necrosis and bullae formation. Local bleeding and ecchymotic patches may develop due to hemostatic defects. Severe limb pain, absence of arterial pulse and cold limb suggest compartment syndrome (due to raise in the pressure of facial compartments which block the arteries) and may lead to ischemia and gangrene of the limb. Other complications like secondary infections, tetanus and gas gangrene may also develop.

Neurotoxicity

- Neurotoxic features are prominently seen with Elapidae bites (cobra, krait, coral snakes). Features start within 6 hrs but may be delayed.
- Paralysis first appears as bilateral ptosis followed sequentially by bilateral ophthalmoplegia, paralysis of muscles of palate, jaw, tongue, larynx, neck and muscles of deglutition. Pupillary reflexes are preserved till late stages. Diaphragm paralysis causes respiratory failure. Patients may become drowsy which may progress to coma. Neurotoxic effects are completely reversible, either spontaneously over several days or weeks, or immediately with anti-snake venom and anticholinesterases (neostigmine).

Cardiotoxicity

- Features include tachycardia, hypotension, and ECG changes. Myocarditis can lead to congestive cardiac failure. Myocardial infarction and sudden cardiac arrest may occur due to dyselectrolytemia.

Hemostatic Abnormalities

- These are due to hemorrhagins and consumption coagulopathy (DIC). Manifestations include bleeding from wound site, gums, nose and venepuncture site. Ecchymoses and bruising are common in the bitten limb. Hemoptysis, hematemesis, hematuria, and intracranial hemorrhage can also occur. Severe bleeding may lead to hypotension and shock. DIC with multiorgan dysfunction including ARDS can occur. Infarction of the anterior pituitary may occur causing acute pituitary adrenal insufficiency, or in survivors, chronic panhypopituitarism.

Nephrotoxicity

- Acute kidney injury commonly occurs in viper bites.

Myotoxicity

- Manifestations are generalized muscle pain, stiffness and myoglobinuria. Rhabdomyolysis is a prominent feature of sea snakebites.

Investigations

- Snake venom detection kits are available in some countries. The venom is detected from a dry swab of the bite site using monoclonal antibody techniques.
- *20-minute whole blood-clotting test*: 2 to 3 ml of venous blood is kept undisturbed in a bottle for at least 20 minutes. Absent coagulation indicates hemostatic defect from systemic envenomation.
- PT and aPTT may be elevated.
- *Full blood count*—anemia may be present due to bleeding. Total WBC is elevated.
- Urea and creatinine may be elevated due to AKI.
- *Electrolytes*—hyperkalemia may be present due to renal failure, hemolysis and rhabdomyolysis.
- Liver function tests may be altered.
- Creatine kinase may be high due to rhabdomyolysis.
- Troponins may be elevated due to myocardial damage.
- Blood grouping, typing and cross-matching as both venom and ASV can interfere with cross-matching.
- Urine examination may show RBCs, RBC casts, protein and myoglobin.
- ECG may show arrhythmias or changes due to electrolyte abnormalities.

Management of Snakebite

Field Management

- Apply a splint to the bitten limb to immobilize it. Immobilization reduces the spread of poison.
- Application of pressure bandage—it limits the spread of poison, but concentrates the poison locally leading to greater local tissue damage and increased risk of amputation and loss of function, particularly with necrotic venoms such as viper venom. Pressure bandage can be used in elapid bites which are primarily neurotoxic without much local effect. Pressure bandage is applied by wrapping the entire limb with a bandage (e.g. crepe or elastic). The wrap pressure must reach ~40–70 mm Hg to be effective.
- Application of tourniquet is not recommended as most of the time it is not applied properly.
- Incision, cauterization and sucking out of venom are not recommended as they are not effective in removing poison and lead to more bleeding and local tissue damage.

- Transport the victim to a hospital as early as possible.
- The best first aid advice, as coined by Dr Ian Simpson of the WHO's snakebite treatment group, is to "do it 'RIGHT'": **R**eassure the victim, **I**mmobilize the extremity, **G**et to the **H**ospital, and inform the physician of **T**elltale symptoms and signs.

Hospital Management

- Blood pressure, heart rate, respiration, coagulation, renal, and neurological status must be monitored.
- *Administration of anti-snake venom (ASV)*—this is the most important step. ASV should be given as soon as possible. ASV is most effective if given within 4 hrs of bite, but can be given up to 24 hrs or longer. Beneficial effects are reported even up to 7–10 days.
- ASV may be monovalent (effective against a particular snake species) or polyvalent (effective against several species).
- Initially a test dose is given by injecting 0.02 ml of saline-diluted ASV, intradermally at a site distant from the bite. The injection site is then observed for at least 10 minutes for the development of redness, hives, pruritus or other adverse effects. However, a negative skin test does not rule out a reaction following administration of the full dose of ASV. Hence, adrenaline injection (epinephrine) should be kept ready whenever ASV is administered. If the risk of allergic reaction is significant, pretreatment with IV antihistamines (e.g. diphenhydramine) and hydrocortisone may be considered. If the patient develops an acute reaction to ASV, infusion should be temporarily withheld and IM epinephrine and IV antihistamine and steroids should be given. ASV should be further diluted in normal saline and restarted at a slower rate.

Indications for Antivenom

Evidence of systemic envenomation
- Neurotoxicity
- Coagulopathy
- Rhabdomyolysis
- Persistent hypotension
- Renal failure

Evidence of severe local envenomation
- Local tissue destruction
- Swelling
- Pain

Dosage of ASV

- *Local reaction only at the site of bite*: 5 vials.
- *Local reaction with severe cellulitis*: 5 to 15 vials.
- *Severe reactions with systemic envenomation*: 15 to 30 vials.
- The recommended initial dose of ASV is 8–10 vials administered over 1 hour as IV infusion in 5% dextrose or normal saline, at the rate of 5–10 ml/kg body weight or as slow IV injection as 2 ml/minute.
- The newest available antivenom in the United States (CroFab) is an ovine, Fab fragment antivenom which is effective against all North American pit vipers. It requires less dosing and carries very low risk of allergic reactions.

Supportive Measures

- IV fluids for hypotension and shock.
- Inj tetanus toxoid 0.5cc IM if not given in last 5 years.
- Antibiotics—gram-negative and anaerobic organisms should be covered. Augmentin plus metronidazole may be used intravenously. Antibiotics are not required routinely. They are required if there is significant local tissue damage with risk of infection.
- Fresh blood or FFP transfusion if bleeding manifestations occur.
- If neuromuscular paralysis is present, Neostigmine 1 mg IV stat plus atropine 1 mg IV should be given. It is repeated every half hourly and then taperd to hourly, 2nd hourly, and 4th hourly. It is most useful when there is respiratory muscle weakness pending ventilatory support and ASV administration.
- Artificial ventilation for respiratory paralysis.
- Surgical debridement for local necrosis and skin grafting.

Q. Scorpion stings.

- More than 80 species of scorpions are seen in India. Most important are black scorpions and red scorpions. Red scorpion is the most dangerous type. Stings occur most commonly at night, on the extremities.
- Scorpion venoms contain neurotoxins which stimulate synaptic sodium and potassium channels with release of catecholamines and acetylcholine.

Clinical Features

Local Features

- Most scorpion bites produce only local features.
- Severe local pain radiating throughout the affected dermatome.
- Swelling.

Systemic Features

- Red scorpion bites can cause severe systemic envenomation.
- Symptoms are due to cholinergic and adrenergic stimulation.

- Cholinergic symptoms include vomiting, increased gastrointestinal motility, profuse sweating, hypersalivation, pupillary constriction, bronchoconstriction, increased secretion of lacrimal, bronchial and pancreatic acinar glands, bradycardia, hypotension and priapism.
- Adrenergic features are hypertension, tachycardia, heart failure and pulmonary edema. Intracranial hemorrhage and convulsions may occur due to severe hypertension.
- In later stages, hypotension and shock may develop.
- ECG may show features of myocarditis or ischemia.
- Urinary excretion of vanillyl mandelic acid (VMA) is increased and cardiac enzymes are elevated.

Treatment

- Severe local pain is treated by injection of local anesthetic (0.1% lignocaine). Systemic analgesics (NSAIDs and opiates) may be needed.
- Hypertension and pulmonary edema are treated by selective α_1-adrenergic blockers such as prazosin.
- Tachycardia is treated with intravenous metoprolol or esmolol.
- Hypotension may require fluid resuscitation.

Q. Discuss the clinical features, diagnosis and management of organophosphorus or carbamate poisoning.

Q. Intermediate syndrome.

- The most common mode of poisoning in India is with organophosphorus (OP) compounds because of their wide availability.
- OP compounds are widely used as pesticides in agriculture. OP nerve agents are used in chemical warfare.
- Carbamates were synthesized after OP compounds. The use of OP compounds has declined after the introduction of carbamates.

Organophosphorus compounds
- *Insecticides*: Dichlorvos, fenthion, malathion, methamidophos, chlorpyrifos, diazinon, parathion, quinalphos
- *Nerve agents*: Sarin, tabun, soman

Carbamates
- Carbaryl, aldicarb and propoxur

Mechanism of Toxicity

- OP compounds are well absorbed through the skin, lungs, and gastrointestinal tract. They inactivate the enzyme acetylcholinesterase (AChE) by phosphorylation leading to the accumulation of acetylcholine (ACh) at cholinergic synapses. After some time, the acetlycholinesterase—OP compound undergoes a conformational change, known as "aging", which renders the enzyme irreversibly resistant to reactivation by oximes.
- Unlike OP compounds, carbamates are transient acetylcholinesterase inhibitors, which spontaneously hydrolyze from acetylcholinesterase site within 48 hours. Hence, carbamate toxicity tends to be of shorter duration than that caused by equivalent doses of organophosphates. However, the mortality rates are similar to OP compounds.
- Recovery follows the reappearance of active AChE following synthesis or spontaneous hydrolysis of phosphorylated AChE.

Clinical Features

- Clinical features can be divided into following 3 phases:
  - Acute cholinergic phase
  - Intermediate syndrome (IMS)
  - Organophosphate-induced delayed polyneuropathy (OPIDN).

Acute Cholinergic Phase

- This is due to acetylcholine excess at the synapses. Symptoms usually start within one hour of exposure.
- Features of cholinergic excess can be divided into muscarinic, nicotinic and CNS manifestations.

Muscarinic Manifestations

- Miosis, blurring of vision.
- Increased lacrimation.
- Increased salivation.
- Vomiting and fecal incontinence due to excess GI motility.
- Increased frequency of micturition.
- Bradycardia, conduction blocks.
- Bronchorrhea, bronchospasm, and pulmonary edema.
- The muscarinic signs can be remembered by the mnemonic DUMBELS—**D**efecation, **U**rination, **M**iosis, **B**ronchorrhea/**B**ronchospasm/**B**radycardia, **E**mesis, **L**acrimation, and **S**alivation.

Nicotinic Manifestations

- Fasciculations.
- Muscle weakness and paralysis due to depolarizing block at neuromuscular junctions similar to succinylcholine.

CNS Manifestations

- Anxiety, restlessness, unconsciousness, convulsions.

Intermediate Syndrome (IMS)

- This begins 1 to 3 days after exposure. It usually occurs after the acute cholinergic phase, but may occur along with it.

- There are several postulations regarding the mechanism of intermediate syndrome: Persistence of nicotinic effects due to lack of early use of oximes; release of organophosphates from the adipose tissue acting on the nicotinic receptors; and neuromuscular junction dysfunction.
- Manifestations are mainly neurological and include weakness of neck muscles, decreased deep tendon reflexes, cranial nerve abnormalities, proximal and respiratory muscle weakness or paralysis. If endotracheal intubation and ventilation are not instituted early, respiratory failure and death may occur. Paralysis may continue for 2–18 days. Recovery from IMS is complete with adequate ventilatory care unless OPIDN develops.

Organophosphate-induced Delayed Neuropathy (OPIDN)

- This occurs about 1 to 3 weeks after acute OP exposure. Agents like triorthocresyl phosphate and chlorpyrifos are frequently associated with OPIDN. Carbamates are only rarely associated with OPIDN. It is due to degeneration of long myelinated nerve fibers.
- Affected patient presents with transient, painful "stocking-glove" paresthesias followed by a symmetrical motor polyneuropathy characterized by flaccid weakness of the lower limbs, which ascends to involve the upper limbs. Sensory loss is often mild. Recovery from OPIDN is usually incomplete.

Diagnosis

- History and examination findings.
- Plasma cholinesterase levels are reduced to less than 50% of normal.

Management

General Measures

- Further exposure is prevented by removing the contaminated clothing and contact lenses.
- Patient is admitted to ICU and vital parameters are continuously monitored.
- Oxygen.
- Gastric lavage.
- Activated charcoal.
- IV fluids.
- Endotracheal intubation and ventilator support if required.

Specific Measures

- Atropine antagonizes the muscarinic effects of acetylcholine. Atropine does not reverse nicotinic effects such as muscle fasciculation. Initially 2 to 5 mg is given IV. If no effect is noted, the dose is doubled every three to five minutes until the muscarinic signs and symptoms are reversed. Atropine infusion is usually required for several days after the exposure. Signs of adequate atropinization are tachycardia, dilatation of pupils, and dryness of mucous membranes. Excess atropine causes agitation, confusion, urinary retention, ileus, and hyperthermia.
- Oximes such as pralidoxime (PAM) and obidoxime are cholinesterase reactivating agents and are effective in treating both muscarinic and nicotinic effects of OP compound. Dose of PAM is 2 g IV infusion over 30 minutes. Oximes are more effective in poisoning due to compounds which age slowly such as diethyl compounds.
- Magnesium sulphate blocks ligand-gated calcium channels, resulting in reduced acetylcholine release from pre-synaptic terminals, thus improving function at neuromuscular junctions, and reduced CNS overstimulation mediated via NMDA receptor activation. Intravenous $MgSO_4$ (4 g) given on the first day after admission has been shown to decrease hospitalization period and improve outcomes in patients with OP poisoning.
- Intermediate syndrome is treated by ventilator support.
- There is no specific therapy for OPIDN. Regular physiotherapy may reduce deformities and muscle-wasting.

Q. Discuss the clinical features and management of sedative-hypnotic (benzodiazepines, barbiturates) overdose.

- Sedative-hypnotics are a group of drugs that cause CNS depression. These drugs include benzodiazepines, barbiturates, and other sleeping pills such as zolpidem and zaleplon.

Mechanism of Action

- All the sedative-hypnotics are general CNS depressants. Most stimulate the activity of GABA, an inhibitory neurotransmitter in the CNS.

Clinical Features of Acute Intoxication

- Clinical features are mainly due to CNS depression and include the following:
  - Slurred speech.
  - Incoordination and unsteady gait.
  - Impaired attention or memory.
  - Impaired consciousness ranging from stupor to coma.
  - Nystagmus and decreased reflexes.
  - Severe overdose may lead to respiratory depression.

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- Psychiatric manifestations include inappropriate behavior, labile mood, and impaired judgment and social functioning.
- Bradycardia and hypotension.
- Bullous skin lesions may be seen in barbiturate poisoning in addition to above features.

Investigations

- Complete blood count (CBC).
- Arterial blood gas (ABG).
- Blood glucose, electrolytes.
- ECG.
- Toxicology screen.

Management

General Measures

- Patient is admitted to ICU and vital parameters are continuously monitored.
- Oxygen.
- Gastric lavage is not advised in pure benzodiazepine overdose. However, it is required in mixed and other sedative hypnotic drug poisoning.
- Activated charcoal. Repeated doses are necessary in barbiturate poisoning.
- IV fluids.
- Endotracheal intubation and ventilator support if required.

Specific Measures

- *Benzodiazepines*—flumazenil is a benzodiazepine antagonist which can be used in acute benzodiazepine intoxication. The starting dose of flumazenil is 0.2 mg intravenously (IV) over 30 seconds. Further doses of 0.5 mg may be given every 60 seconds up to a total of 5 mg. It can provoke withdrawal seizures in patients with benzodiazepine dependence.
- *Barbiturates*—alkaline diuresis and hemodialysis are helpful in enhancing barbiturate removal.

Q. Aluminum and zinc phosphide poisoning.

- Aluminum phosphide is a solid fumigant pesticide available in tablet form (sometimes referred to as rice tablets). Zinc phosphide usually comes as a black powder. Both are used to protect grains from pests and rats. Poisoning is most common in the post harvest season from July to September.
- The following description applies to both aluminum and zinc phosphide.

Mechanism of Toxicity

- After ingestion, aluminum phosphide reacts with water in the stomach to release phosphine gas which has local as well as systemic toxicity.
- Local effects are severe burning retrosternal pain and vomiting. Systemic toxicity occurs after absorption from GI tract.
- Mechanism of systemic toxicity include cellular hypoxia due to the effect on mitochondria, inhibition of cytochrome C oxidase and formation of highly reactive hydroxyl radicals. This leads to multiorgan dysfunction such as cardiac failure due to myocarditis, hypotension, renal damage, liver cell necrosis, acute lung injury, and metabolic acidosis.
- Hypo- or hypermagnesemia can occur.

Diagnosis

- Detecting phosphine in the exhaled air or stomach aspirate by using silver nitrate-impregnated strip or gas chromatography.

Management

- Gastric lavage with $KMnO_4$ (1:10000) or with magnesium sulphate ($MgSO_4$) to oxidize the unabsorbed poison. Gastric lavage with coconut oil has also been found to be helpful.
- Activated charcoal orally or through nasogastric tube to adsorb phosphine from the gastrointestinal tract.
- Antacids or H_2 blockers to reduce burning pain in the stomach and to reduce the absorption of phosphine.
- Magnesium sulfate ($MgSO_4$) is very effective in counteracting the toxic effects of aluminum phosphide. Magnesium has anti-hypoxic, anti-arrhythmic, and antioxidant properties, hence is effective in reducing the morbidity and mortality of aluminum phosphide poisoning. Dose is 1 g IV stat, followed by 1 g every 4–6 hours for 5 to 7 days.
- Sodium bicarbonate infusion can be given to correct metabolic acidosis.
- Mortality is high and most patients die despite optimal supportive care.

Q. Paracetamol (acetaminophen) poisoning.

- Paracetamol poisoning is common because of its wide availability as an over-the-counter drug.
- Maximum recommended daily dose is 4 g in adults.
- Toxicity is likely to occur at doses greater than 250 mg/kg per day. Almost all patients who ingest >350 mg/kg develop severe liver toxicity.

Mechansim of Toxicity

- Paracetamol is metabolized by conjugation in the liver to nontoxic compounds. In acute overdose, metabolism by conjugation becomes saturated, and excess paracetamol is oxidatively metabolized by the CYP enzymes to the hepatotoxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI) which causes hepatic injury.

Clinical Features

- Initial complaints are nausea, vomiting, diaphoresis, pallor, lethargy, and malaise.
- Liver damage usually develops 1 to 3 days after ingestion. Jaundice, hepatic encephalopathy, hyperammonemia, bleeding diathesis and marked elevation of liver enzymes (AST and ALT >1000 IU/L) develop.
- Rarely, renal failure and acute pancreatitis may occur.
- Confirmation of diagnosis and severity of poisoning can be assessed by measurement of serum paracetamol levels.

Management

- Gastric lavage.
- Activated charcoal.
- The antidote is N-acetylcysteine (NAC), which is most effective if given within 10 hours of the overdose. It can be given either orally or intravenously. Oral regimen is loading dose of 140 mg/kg stat followed by 17 doses of 70 mg/kg given every 4 hours .
- Methionine 12 g orally 4th hourly, to a total of four doses, is an alternative if NAC is not available.
- Liver transplantation should be considered in patients who develop acute liver failure.

Q. Salicylate (aspirin) poisoning.

- Aspirin is widely used as antiplatelet agent in patients with cardiovascular and cerebrovascular disease.
- Aspirin (acetylsalicylic acid) is rapidly converted to salicylic acid in the body. Other salicylates, such as salicylic acid (a topical keratolytic agent and wart remover) and methyl salicylate (oil of wintergreen), can also cause intoxication when ingested.
- Ingestion of greater than 150, 250 and 500 mg aspirin/kg body weight produces mild, moderate and severe poisoning, respectively.

Clinical Features

- Nausea and vomiting due to irritation of the gastric mucosa and stimulation of the chemoreceptor trigger zone.
- Tinnitus and deafness.
- Hyperventilation due to direct stimulation of the respiratory center leading to respiratory alkalosis. Metabolic acidosis occurs due to interference with cellular metabolism. But the net effect is respiratory alkalosis in most adults.
- Petechiae and subconjunctival hemorrhages can occur due to reduced platelet aggregation.
- Renal failure and CNS effects such as agitation, confusion, coma and fits can occur in severe poisoning. Rarely, pulmonary and cerebral edema occur.
- Death can occur as a consequence of CNS depression and cardiovascular collapse.
- Plasma salicylate concentration helps in assessing the severity of poisoning. It should be measured 6 hours or later after ingestion because of continued absorption of the drug.

Management

- Multiple doses of activated charcoal.
- Metabolic acidosis is treated with intravenous sodium bicarbonate to maintain an arterial pH of 7.4–7.5.
- Dehydration is treated by intravenous fluids.
- Urinary alkalinization enhances the clearance of salicylate.
- Hemodialysis is very effective at removing salicylate and should be considered if there is cerebral or pulmonary edema, renal failure or serum salicylate concentration is >100 mg/dl.

Q. Cyanide poisoning.

- Cyanide is among the most rapidly lethal poisons known to man. It causes death within minutes to hours of exposure.
- Cyanide exists in gaseous, liquid, and solid forms. Depending on its form, cyanide may cause toxicity through inhalation, ingestion, dermal absorption, or parenteral administration. Smoke inhalation, suicidal ingestion, and industrial exposures are the most frequent sources of cyanide poisoning. Inhalation of hydrocyanic acid or ingestion of inorganic cyanide salts or cyanide releasing substances such as cyanamide result in poisoning. Infusion of sodium nitroprusside used in hypertensive emergencies can also cause cyanide toxicity. Amygdala from bitter almonds also releases cyanide on digestion.

Mechanism of Toxicity

- Cyanide is a mitochondrial toxin. It inhibits cytochrome oxidase in the mitochondria leading to stoppage of oxidative phosphorylation resulting in histotoxic anoxia,

leading to cellular dysfunction and death. There is formation of lactic acid and the development of metabolic acidosis due to anaerobic metabolism.

Investigations

Arterial and Venous Blood Gases

- Arterial oxygen tension is normal and venous oxygen tension is abnormally high due to nonutilization of oxygen by cells, resulting in a decreased arteriovenous oxygen difference (<10%). A high-anion-gap metabolic acidosis is seen due to lactic acidosis as a result of anaerobic metabolism.

Blood Lactate Level

- Elevated due to anaerobic metabolism. It is a sensitive marker for cyanide toxicity.

RBC or Plasma Cyanide Concentration

- The preferred test is red blood cell cyanide concentration. This test can be used for confirmation of cyanide poisoning, but results may not be available early to start treatment.

Methemoglobin Level

- Presence of methemoglobin in the blood is reassuring because it indicates that there is no free cyanide available for binding, because methemoglobin vigorously binds cyanide to form cyanomethemoglobin.
- Methemoglobin level can also be used a guide for the use of methemoglobin-inducing antidotes, such as sodium nitrite. Elevated level of methemoglobin (>10%) indicate that further nitrite therapy is not indicated.

Clinical Features

- There may be characteristic smell of bitter almonds.
- After inhaling cyanide, there is headache, anxiety, nausea, and a metallic taste. There may be eye and mucous membrane irritation, bronchorrhea, cough, and dyspnea.
- Ingestion of cyanide salts results in gastric irritation, causing vomiting and abdominal pain.
- Multiorgan failure—renal failure, hepatic necrosis, pulmonary edema, rhabdomyolysis.
- Skin appears flushed and cherry-red due to non-utilization of oxygen by cells.
- Convulsions, coma and death occur within a few hours.

Treatment

- Gastric lavage.
- Activated charcoal.
- Hydroxocobalamin, a precursor of vitamin B_{12}, contains a cobalt moiety which binds to cyanide, forming cyano-cobalamin. This molecule is stable, with a few side effects, and is easily excreted in the urine. Hydroxocobalamin is considered the first choice therapy for cyanide poisoning. It is given intravenously. Combination of hydroxo-cobalamin and sodium thiosulfate is effective and safe in severe cyanide poisoning.
- *Taylor cyanide antidote package*: It contains amyl nitrite, sodium nitrite and sodium thiosulfate. Amyl nitrite is inhaled followed by IV injection of sodium nitrite. These drugs induce methemoglobinemia, which binds to cyanide to form less toxic cyanomethemoglobin. Sodium nitrite should be followed by intravenous injection of sodium thiosulfate. Sodium thiosulfate converts cyanide to thiocyanate, which is easily excreted by kidneys.
- Dicobalt edetate is an intravenous chelator of cyanide. It has severe side effects, and is used only when other agents are not available.

Q. Methanol (methyl alcohol) poisoning.

- Methanol (wood alcohol) is used as a denaturant and is a component of varnishes, paint removers, windshield washers, copy-machine fluid, antifreeze solutions, and industrial solvents.
- Ingestion of methyl alcohol usually occurs with ingestion of cheap illicit liquor (hooch). The toxic dose is 30 ml of a 40% solution.

Mechanism of Toxicity

- Methanol itself is not very toxic except CNS depression.
- Toxicity is mainly due to its metabolites such as formaldehyde and formic acid which are produced by alcohol dehydrogenase.

Clinical Features

- Initial manifestations are due to methanol itself and include inebriation, gastritis, abdominal pain, nausea and vomiting. High dose causes obtundation, convulsions and coma.
- Late manifestations are due to formic acid and include retinal injury, metabolic acidosis, seizures, coma and death. Ocular toxicity manifests as diminished vision, flashing spots, dilated or fixed pupils, hyperemia of the optic disc, retinal edema and blindness.

Investigations

- Serum methanol levels.
- Arterial blood gas (ABG) shows high anion gap metabolic acidosis.

- Renal function tests and liver function tests.
- CT scan of the brain shows bilateral putamen necrosis.

Management

General Measures

- Correction of acidosis by sodium bicarbonate infusion.
- Gastric lavage is useful if performed within 1 hour of ingestion. Activated charcoal is not useful.
- Control of seizures.
- IV fluids.

Specific Measures

- Ethanol is given to saturate alcohol dehyrogenase in the liver and prevent the formation of the toxic metabolites of methanol. A 5% solution of ethanol is prepared; 15 ml/kg is given as a loading dose and than 2–3 ml/kg/ has maintenance dose. It can be given orally also.
- Fomepizole (4-methylpyrazole) blocks alcohol dehydrogenase and can be used instead of ethanol.
- Hemodialysis should be done if there is severe metabolic acidosis, or evidence of end-organ damage (e.g. visual changes, renal failure).

Q. Opioid/morphine poisoning.

- Opioids include heroin, morphine, methadone, codeine, pethidine, dihydrocodeine and dextropropoxyphene. Heroin (diacetylmorphine, diamorphine) is an artificial alkaloid derived from morphine, is the most dangerous drug of addiction.
- Opioids are commonly used as drugs of abuse. They give a rapid, intensely pleasurable experience, often accompanied by heightened sexual arousal. Physical dependence occurs within a few weeks of regular use.
- Overdose may occur due to therapeutic use, recreational use, intended self-harm, attempt to hide drugs from law enforcement agencies ("body stuffing"), swallowing packaged drugs in order to transport them across borders ("body packing"), and unintentional pediatric exposures.

Clinical Features of Overdose

- The classic signs of opioid intoxication include:
  - Decreased conscious level.
  - Decreased respiration.
  - Decreased bowel sounds.
  - Decreased pupil size (pinpoint pupils).
- There may be signs of intravenous drug abuse (e.g. needle track marks).
- Severe poisoning is indicated by respiratory depression, hypotension, ARDS and hypothermia. Death occurs due to respiratory arrest or aspiration of gastric contents.
- Dextropropoxyphene can also cause ventricular arrhythmias and heart blocks.

Management

General Measures

- Maintenance of airway.
- Supplementary high-flow oxygen.
- Endotracheal intubation and ventilatory support if required.
- Gastric lavage and activated charcoal are usually not indicated because of risk of aspiration.

Specific Measures

- Naloxone is a specific opioid antagonist which reverses the features of opioid toxicity. It is given as IV bolus (0.8–2 mg) and repeated every 2 minutes until the level of consciousness and respiratory rate increase and the pupils dilate. This is followed by intravenous infusion of naloxone.
- Withdrawal symptoms can be managed by substitution with oral methadone.

Q. Oleander poisoning (cerbera thevetia; cerbera odallum; yellow oleander).

- This is an ornamental plant that is grown for its yellow bell-shaped flowers in the gardens of India.
- It contains highly toxic cardiac glycosides which are responsible for various heart blocks, bradyarrhythmias and tachyarrhythmias.
- All parts of the plant contain toxin, but seeds have maximum amount.
- The roots and seeds are used as abortifacients, for suicidal and homicidal purposes and also as cattle poisons.

Clinical Features

- *GI symptoms*—dryness of the throat, vomiting, diarrhea.
- *CNS effects*—dizziness, dilated pupils, muscular weakness, tetanic convulsions.
- *Cardiac effects*—bradycardia, irregular pulse, heart blocks.
- Death may occur from circulatory failure.

Management

- Gastric lavage.
- Repeated doses of activated charcoal.
- Correction of acidosis, fluid and electrolyte disturbances.
- Atropine and pacing for bradycardia and heart blocks.
- Digoxin specific Fab antibodies can be used in severe poisoning.

Q. Datura poisoning.

- *Datura stramonium* (also known as thorn apple, angel's trumpet, Devil's trumpet, Devil's weed, etc.) is a common weed along roadsides, in cornfields and pastures and in waste areas. Its toxic components are tropane belladonna alkaloids which have anticholinergic action. It has been used voluntarily by teenagers for its hallucinogenic effect. Scopolamine, a muscarinic antagonist is thought to be mainly responsible for the toxic anticholinergic effects. The seeds and fruits are the most poisonous parts of the plant.

Clinical Features

- Datura produces anticholinergic syndrome.
- Initial symptoms are dry mouth and throat, burning pain in the stomach and difficulty in swallowing and talking.
- Later, giddiness, ataxia, incoordination of muscles, flushed appearance of the face, dry hot skin, diplopia, dilated pupils with loss of accommodation, reddening of the conjunctiva and drowsiness ensue. Sometimes, an erythematous rash appears all over the body.
- Delirium, stupor, convulsions, and coma occur in severe poisoning.
- Death can occur from respiratory failure.
- Classically the effects of Datura are described as "hot as a hare" (rise in skin temperature), "blind as a bat" (diplopia, loss of accommodation), "dry as a bone" (dryness of mouth, skin), "red as a beet" (cutaneous flushing) and "mad as a hatter" (delirium).

Management

- Gastric lavage with potassium permanganate solution or 5% tannic acid solution.
- Activated charcoal.
- Delirium is treated with sedatives.
- Cholinergic agents such as neostigmine, physostigmine or methacholine may be given to counteract anticholinergic effects of Datura.

Q. Lead poisoning.

- Lead exposure can occur in numerous work settings, such as manufacturing or use of batteries, solder, ammunitions, paint, car radiators, cable and wires, some cosmetics, ceramic ware with lead glazes, tin cans and plumbing. Earlier lead was being added to gasoline and petrol to increase the octane level, but this practice has been discontinued and only unleaded fuel is available now. Lead is also found in some traditional Hispanic and Ayurvedic medicines.
- Lead toxicity usually results from chronic repeated exposure and is rare after a single ingestion. Lead-containing bullets lodged in the body can result in chronic lead toxicity.
- Lead is absorbed from the lungs or gastrointestinal tract. In adults, absorption of lead via the respiratory tract is the most significant route of entry. GI absorption can also be significant, if working and/or eating in a lead-contaminated environment. GI absorption is the predominant route in children.
- Once absorbed, lead is distributed to the blood, soft tissues, and skeleton. In blood, 99% of lead is bound to the erythrocytes.
- Lead is a toxic metal that affects many organ systems and functions in humans. It inhibits sulfhydryl-dependent enzymes such as gamma-aminolevulinic acid dehydratase (ALA-D) and ferrochelatase which are important for heme synthesis. It also interferes with mitochondrial respiration and various nerve functions. Lead can also affect DNA and RNA. Lead has effects on cell membranes, interfering with various energy and transport systems.

Clinical Features

- Colicky abdominal pain, constipation, joint pains, muscle aches, headache, anorexia, decreased libido, difficulty concentrating and deficits in short-term memory, anemia, and nephropathy.
- Coma and convulsions may occur in severe poisoning.
- A bluish lead line may be seen at the gum-tooth line, and is due to reaction of lead with dental plaque.
- Chronic lead poisoning can cause learning disorders (in children) and motor neuropathy (e.g. wrist drop).

Diagnosis

- Whole blood lead levels above 10 μg/dl are considered to be toxic. Level >10 μg/dl for extended period of time is associated with impaired neurobehavioral development in children. Level of >50 μg/dl may be associated with headache, irritability, subclinical neuropathy, colicky abdominal pain, etc. Level greater than 70 μg/dl is often associated with severe poisoning and acute encephalopathy.
- Microcytic anemia with basophilic stippling.
- Elevated free erythrocyte protoporphyrin.
- X-ray fluorescence is a new technology that can be used to make rapid, noninvasive measurements of lead in bone.

Treatment

- Maintain airway and treat coma and convulsions in severe poisoning.

- *Avoid further exposure*—if a large lead-containing object (e.g. fishing weight) has been ingested, it should be removed by repeated cathartics, whole bowel irrigation, endoscopy, or even surgical removal to prevent subacute lead poisoning. Workers with a single lead level greater than 60 µg/dl must be removed from the site of exposure.
- *Chelation therapy*—patients with severe intoxication (encephalopathy or levels greater than 70 µg/dl) should receive calcium EDTA. Dimercaprol (BAL) can be used in addition to EDTA. Patients with less severe symptoms and asymptomatic patients with blood lead levels between 55 and 69 µg/dl may be treated with EDTA alone. An oral chelator, succimer (DMSA-dimercapto-succinic acid) is available for use in children.

Q. Arsenic poisoning.

- Arsenic is a metalloid element. It is tasteless, odorless, and well absorbed after ingestion or inhalation. Common sources of exposure are ground water and food with high arsenic content.
- In exposed individuals, high concentrations of arsenic are present in bone, hair and nails.
- The primary target organs for arsenic toxicity are the gastrointestinal tract, skin, bone marrow, kidneys, and peripheral nervous system.

Mechanism of Toxicity

- Arsenic inhibits the enzyme pyruvate dehydrogenase complex, which catalyzes the oxidation of pyruvate to acetyl-CoA. This leads to disrupted the energy system of the cell resulting in cell death.

Clinical Features

Acute Poisoning

- This can occur after ingestion or inhalation of arsenic dusts or fumes.
- Symptoms may develop within minutes or hours.
- Initially GI symptoms are seen and include nausea, vomiting, abdominal pain, and diarrhea. There may be a garlic odor of the breath and stool.
- These are followed by dehydration, hypotension, irregular pulse and cardiac instability.
- Acute encephalopathy may develop and lead to delirium, coma, and seizures.
- Renal injury can lead to proteinuria, hematuria, and acute tubular necrosis.
- In severe cases, shock, ARDS, and death may occur.
- If patients survive the initial illness, hepatitis, pancytopenia, and sensorimotor peripheral neuropathy may develop.

Chronic Poisoning

- Chronic arsenic exposure from drinking water has been reported in many parts of the world.
- Manifestations are peripheral neuropathy, skin eruptions, hepatotoxicity, bone marrow depression, and increased risk of cancers.
- Mee's lines (transverse white lines on finger nails) may be seen in some.

Management

- Elimination of further exposure.
- Gastric lavage and activated charcoal in cases of ingestion.
- Chelation is indicated in patients with symptomatic arsenic poisoning. Dimercaprol (British Anti-Lewisite, or BAL) and succimer (DMSA) are used as chelating agents.

Q. Enumerate the causes of hyperthermia (hyperpyrexia).

Environmental exposure	Status epilepticus
Cerebral and pontine hemorrhage	Alcohol, sedative-hypnotic withdrawal
Tetanus	Drug overdose (sympathomimetics, anticholinergics)
Thyroid storm	Dystonic reactions
Pheochromocytoma	Serotonin syndrome
Malignant hyperthermia	
Neuroleptic malignant syndrome	

Q. Enumerate various heat related illnesses and the predisposing factors.

- Various heat related illnesses are:
  - Heat syncope
  - Heat cramps
  - Heat exhaustion
  - Heat stroke (heat injury)

Predisposing Factors for Heat Related Illnesses

High temperature
High humidity
Dehydration
Elderly persons and infants
Heavy exercise, particularly in the sun
Heavy clothing
Decreased sweating
Associated infection
Obesity
Alcohol withdrawal
Mental illness
Hyperthyroidism
Drugs (anticholinergics, phenothiazines)

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Q. Heat syncope.

- This is sudden unconsciousness due to cutaneous vasodilation in a hot weather leading to cerebral hypoperfusion. Skin is cool and moist, and there is weak pulse and hypotension.
- Treatment consists of rest and recumbency in a cool place and fluid and electrolyte rehydration by mouth (or intravenously if necessary).

Q. Heat cramps.

- This is due to salt depletion or water intoxication. Salt depletion occurs due to loss in sweat-coupled with inadequate salt intake when a person exercises in hot environment.
- It is characterized by painful skeletal muscle contractions ("cramps") often affecting the extremities. The affected muscles are contracted into stony hard lumps.
- Blood shows hemoconcentration and reduced sodium and chloride concentration.
- Treatment involves moving the person to a cool environment and giving oral saline solution (4 tsp of salt per gallon of water) to replace both salt and water. For severe cramps 0.5 to 1 liter of normal saline is administered intravenously.
- It can be prevented by liberal salt intake.

Q. Heat exhaustion.

- Heat exhaustion is a non-life-threatening clinical syndrome of weakness, malaise, nausea, syncope, and other nonspecific symptoms caused by heat exposure. Thermoregulation and CNS function are not impaired.
- Heat exhaustion results from prolonged exertion in hot weather, profuse sweating and inadequate salt and water replacement.
- There can be pure-water-depletion, salt depletion or combined water and salt depletion.
- Core body (rectal) temperature is usually below 39°C.
- The main differences between heat stroke and heat exhaustion are lesser elevation of core body temperature and absence of severe CNS damage in heat exhaustion. If untreated, heat exhaustion may progress to heat stroke.

Clinical Features

- Features of dehydration such as dryness of tongue and mouth, excessive thirst, tachycardia, hypotension, tachypnea, oliguria and weakness.
- Nausea, vomiting, malaise, and myalgia may occur.
- Tachypnea may lead to tetany.
- Irritability and incoordination may be present. Death may occur due to hypovolemic shock.

Investigations

- Elevation of the blood urea, sodium and hematocrit due to water depletion. Sodium level may be low in salt depletion type heat exhaustion due to water replacement without salt.

Treatment

- Removal of the patient from the heat.
- Active cooling using cool sponging.
- Fluid and salt replacement using oral rehydration mixtures containing both salt and water or intravenous isotonic saline. Hypertonic (3%) saline may be needed for severe hyponatremia.

Q. Heat stroke.

- Heat stroke is defined as a core body temperature in excess of 40°C (105°F) with associated CNS dysfunction in the setting of a large environmental heat load that cannot be dissipated.
- Heat stroke results from a complete breakdown of the thermoregulatory mechanism, with complete failure of sweating. There is widespread cellular damage of vital organs due to high body temperature.

Clinical Features

- There are two types of heat stroke; exertional and non-exertional (classic).
- Exertional heat stroke occurs in healthy individuals who engage in heavy exercise during high ambient temperature and humidity. Typical patients are athletes and military recruits in basic training.
- Nonexertional (classic) heat stroke occurs in individuals with an underlying disorder such as mental illness, hyperthyroidism, obesity, extremes of age, and use of drugs.
- Clinical features are due to shock, renal and liver damage, involvement of CNS and DIC.
- Rectal temperature is 40°C or more.
- Initial manifestations are faintness, dizziness, vertigo, nausea, and abdominal pain.
- CNS manifestations are altered sensorium, seizures and coma.
- Skin is flushed, hot and dry.
- Jaundice and petechiae may be present.
- Tachypnea, and bibasal lung crepitations may be present due to ARDS.
- Excessive bleeding may occur due to DIC.
- Death may occur due to ARDS, DIC, myocardial infarction and acute adrenal insufficiency.

Laboratory Features

- Investigations show hemoconcentration, leukocytosis, elevated urea and creatinine, proteinuria, coagulopathy and DIC, elevated liver enzymes, respiratory alkalosis and metabolic acidosis. Myoglobinuria may be present due to rhabdomyolysis.
- ECG may show non-specific ST depression and T wave inversion.

Treatment

- 100% oxygen.
- Endotracheal intubation and ventilatory support if required.
- *Reduction of body temperature*
  - Augmentation of evaporative cooling is the treatment of choice because it is effective, noninvasive, and easily performed. The naked patient is sprayed with lukewarm water and air is circulated with large fans.
  - Other cooling methods are immersing the patient in an ice-water tub (most rapid method of cooling), covering with watercooled sheets, keeping ice bags over of the body, intravenous or intraperitoneal administration of cool fluid, and gastric lavage or enema with ice-water.
- Hydrocortisone or dexamethasone injection IV 8 hourly helps to correct shock, cerebral edema and adrenal insufficiency.
- Renal failure may require hemodialysis.

Q. Neuroleptic malignant syndrome (NMS).

- Neuroleptic malignant syndrome (NMS) is a life-threatening medical emergency associated with the use of neuroleptic agents such as phenothiazines, butyrophenones and thioxanthines.
- It usually develops during the first two weeks of neuroleptic therapy. It is not a dose-dependent phenomenon, but is an idiosyncratic reaction.

Clinical Features

- NMS is characterized by mental status change, muscular rigidity, hyperthermia, and dysautonomia. The diagnosis should be suspected if any two of these four features appear in the setting of neuroleptic use.
- Mental status changes are delirium with confusion which may evolve to stupor and coma.
- Muscular rigidity is generalized. It can be leadpipe or cogwheel type rigidity. Other motor abnormalities include tremors, dystonia, opisthotonus, trismus, chorea, and other dyskinesias.
- Autonomic instability manifests as tachycardia, labile or high blood pressure, tachypnea, arrhythmias, and increased sweating.

Laboratory Features

- Leukocytosis.
- Elevated creatine kinase (CK) and hyperkalemia due to rhabdomyolysis.
- Elevated liver enzymes.
- Myoglobinuria and acute renal failure.

Treatment

- Neuroleptics should be withheld.
- Supportive measures.
- Temperature should be lowered by external and internal cooling methods.
- Dantrolene and bromocriptine may be considered in severe cases.

Q. Define hypothermia. Discuss the causes, clinical features and management of hypothermia.

- Hypothermia is defined as core body temperature below 35°C. Either rectal or esophageal temperature should be measured, as oral temperature is inaccurate.

Predisposing Factors for Hypothermia

- Elderly persons and infants
- Alcoholics
- Cold weather
- Immersion in cold water
- Mental retardation
- Malnutrition
- Stroke
- Cardiovascular disease
- Hypothyroidism
- Hypopituitarism
- Addison's disease
- Transfusion of large amounts of refrigerated blood
- *Drugs*: Sedatives, phenothiazines

Clinical Features

- Core body temperature is below 35°C.
- Early manifestations are weakness, drowsiness, lethargy, irritability, confusion, shivering, and impaired coordination.
- Below 30°C there is cessation of all cerebral activity. Pulse and respiration become slow.
- Below 27°C, patient becomes unconscious, and deeply comatose at 25°C. Pulse and BP may be unobtainable, leading clinicians to believe that the patient is dead.

- Skin may appear blue or puffy.
- Other features are pulmonary edema, sluggish reflexes and generalized rigidity.
- Metabolic acidosis, pneumonia, pancreatitis, ventricular fibrillation, hypoglycemia or hyperglycemia, coagulopathy, and renal failure may occur.
- Death is usually due to cardiac asystole or ventricular fibrillation.

Investigations

- Hemoconcentration.
- Hyperkalemia.
- Arterial blood gas (ABG) analysis may show low paO_2 and metabolic acidosis.
- ECG may show characteristic J waves of Osborn (positive deflection in the terminal portion of the QRS complex) and prolongation of the PR, QRS, and QT intervals.
- SGOT and CK may be elevated due to muscle damage.
- Serum amylase may be elevated due to pancreatitis.
- If the cause of hypothermia is not obvious, additional tests may be done to identify any predisposing condition.

Management

- Goals of treatment are to rewarm the patient in a controlled manner and to treat the associated abnormalities.
- Any underlying condition should be treated promptly (e.g. hypothyroidism).

Mild Hypothermia (Core Temperature >32°C)

- Patient should be put in a warm room, and given additional thermal insulation (blankets and/or space film blanket). They should be given warm drinks. Core temperature will rise slowly over a few hours as a result of normal metabolic heat production.

Severe Hypothermia (Core Temperature <32°C)

- Patients should be handled gently and maintained in a horizontal position to avoid precipitating cardiac arrhythmias.
- Active external or internal rewarming methods are used to raise the core body temperature.
- Active external rewarming methods include heated blankets, forced hot air, radiant heat, and warm baths.
- Active internal rewarming methods include extracorporeal blood rewarming (method of choice), peritoneal or hemodialysis using warm dialysate fluid, administration of warm IV fluids, administration of heated, humidified air warmed to 42°C through a face mask or endotracheal tube, and gastric lavage with warm fluid.

Q. Discuss briefly the various cold related illnesses.

- *Various cold related illnesses are*
  - Frostbite (freezing cold injury).
  - Trench or immersion foot (non-freezing cold injury).
  - Chilblains.

Frostbite (Freezing Cold Injury)

- Frostbite results from the freezing of tissue and usually affects the exposed parts of the body such as fingers, toes, ears and face. It usually occurs in mountaineers, soldiers, those who work in the cold, the homeless, and individuals stranded outdoors in the winter.
- Tissue destruction occurs due to formation of ice crystals and subsequent inflammatory process.
- Predisposing factors are same as those listed under hypothermia.

Clinical Features

- Frostbitten tissue is initially pale and doughy to the touch and insensitive to pain. Once frozen, the tissue is hard.
- Other features are edema, hemorrhages, blisters and blebs.
- Local gangrene may occur.

Treatment

- *Rewarming*—this is done by immersing the affected area in a waterbath heated to 40° to 42°C. Higher temperatures may result in burns. Rubbing and direct heat should be avoided as they may exacerbate tissue injury. Thawing is usually complete in 15 to 30 minutes. Rewarming of frostbitten tissue is painful, hence, analgesics, generally opioids, should be administered.
- Tetanus prophylaxis, protection of the injured tissue and avoidance of infection.
- Because frostbite is associated with vascular thrombosis of the affected tissue, intravenous heparin along with thrombolytics (tPA) may improve outcome and prevent future amputation.
- Surgery may be required to remove dead tissue, but should be delayed, as surprisingly good recovery may occur over an extended period.

Non-freezing Cold Injury

Trench or Immersion Foot

- This is caused by prolonged immersion in cool or cold water or mud, usually less than 10°C. Foot is commonly affected.
- Initial symptoms are cold and numbness, but there is no freezing of the tissue. Later manifestations are edema, blistering, swelling, redness, ecchymoses, hemorrhage,

necrosis, peripheral nerve injury, or gangrene and secondary complications such as lymphangitis, cellulitis, and thrombophlebitis.
- Treatment involves gradual rewarming and recovery is usually complete. Tetanus prophylaxis is required.

Chilblains (Pernio)

- Chilblains or erythema pernio are inflammatory skin changes caused by exposure to cold without actual freezing of the tissues. Pernio is most common in young women, but both sexes and all age groups may be affected.
- Lesions are edematous, reddish or purple, painful or pruritic, with burning or paresthesias. With continued exposure, ulcerative or hemorrhagic lesions may appear and progress to scarring, fibrosis, and atrophy.
- Treatment involves slow and passive rewarming of the affected part. Prazosin, 1 mg orally daily is useful for treatment and prevention of recurrence. Nifedipine is useful for pain.

Q. Drowning.

- Drowning refers to death due to immersion in water. Near drowning describes a submersion event leading to injury without death.
- In about 10% of cases no water enters the lungs but death may occur due to intense laryngospasm ('dry' drowning).
- Drowning is a common cause of accidental death throughout the world and is particularly common in young children.
- Drowning is more common in males and during summer months.

Conditions that Increase Risk of Submersion Injury

- Use of alcohol or other sedative drugs.
- Extreme fatigue.
- Hyperventilation.
- Sudden acute illness (e.g. hypoglycemia, seizure, arrhythmia, myocardial infarction).
- Muscle cramps while swimming.
- Acute brain or spinal cord injury.
- Venomous stings, bites, or injury in the water.

Pathogenesis of Drowning

- Inhalation of water into the lungs leads to diffuse pulmonary edema, ARDS, ventilation-perfusion mismatching and intrapulmonary shunting, leading to hypoxemia. Hypoxemia causes diffuse organ dysfunction.
- Fresh water is hypotonic, and if absorbed into circulation in large amounts, may lead to hemolysis. Sea water is hypertonic and draws plasma into the alveoli leading to alveolar edema.
- Both salt water and fresh water wash out surfactant, leading to alveolar collapse and ventilation perfusion mismatching.
- Infection may occur if drowning occurs in contaminated water.
- Prolonged immersion in cold water may lead to hypothermia.
- Survival is possible after immersion for periods of up to 30 minutes in very cold water particularly in children.

Clinical Features

- Patients are often unconscious with absent breathing and may be in shock. Patients usually have anxiety, dyspnea, cough, wheezing, trismus, cyanosis, chest pain, arrhythmia, hypotension, vomiting, and diarrhea. A pink froth from the mouth and nose indicates pulmonary edema.
- *RS*—breathlessness, crepitations, and wheezing due to pulmonary edema and ARDS. Hemoptysis may occur due to alveolar damage.
- *Nervous system*—patients are in altered sensorium or unconscious due to cerebral hypoxia. Neuronal damage may lead to cerebral edema and raised ICT.
- *CVS*—hypothermia and hypoxemia can lead to arrhythmias. Sinus bradycardia and atrial fibrillation are common. Ventricular fibrillation or asystole may rarely occur.
- *Renal*—renal failure due to acute tubular necrosis may occur due to hypoxia, shock, hemoglobinuria, or myoglobinuria.

Laboratory Features

- Chest X-ray may show pulmonary edema or ARDS.
- ABG shows hypoxemia.
- ECG may show arrhythmias.
- Metabolic acidosis may be present.
- Hypernatremia may occur due to absorption of swallowed seawater.

Management

- Cardiopulmonary resuscitation if pulse and respiration absent. Basic life support (BLS) protocol to be followed.
- Administration of oxygen.
- Airway should be cleared of foreign bodies. There is no need to try to drain the lungs of water since most inhaled water would have been absorbed.
- Intubation and ventilator support may be required for those unable to maintain oxygen saturation even after

oxygen supplementation. Continuous positive airways pressure (CPAP) is useful in improving arterial oxygenation for spontaneously breathing patients.

- Cardiovascular support: Central venous pressure must be monitored to determine the intravascular volume status. Fluid overload and pulmonary edema should be treated with diuretics. Inotropic agents such as dopamine or noradrenaline should be used for persistent hypotension inspite of adequate intravascular volume.
- Prophylactic antibiotics are required only if drowning took place in contaminated water.

Q. Hanging.

- Hanging is a form of strangulation that involves suspension by the neck. Hangings can be complete or incomplete. In complete hanging, feet do not touch the ground and the entire weight of the victim is suspended at the neck. In incomplete hanging (partial hanging), some part of the body is touching the ground and the weight of the victim is not fully supported by the neck. Hanging may be suicidal, homicidal, accidental or judicial.

Pathophysiology

- The following mechanisms are responsible for morbidity and mortality seen in cases of hanging.
- Fracture of the upper cervical spine (fracture of C_2 in the classic hangman fracture), and transection of the spinal cord. This is especially seen in judicial hanging where the body is dropped from a height. Partial injury to the spinal cord can also occur.
- Venous and arterial (carotids) obstruction, leading to cerebral edema, hypoxia, and unconsciousness, which in turn, produces loss of muscle tone and airway obstruction.
- Vagal collapse, caused by pressure to the carotid sinuses and increased parasympathetic tone.

Clinical Features

- Cough, stridor, muffled voice, respiratory distress and hypoxia may be present.
- Altered mental status.
- Abrasions, lacerations, contusions, edema and ligature mark may be observed on the neck.
- Subconjunctival hemorrhage and petechial spots may be seen in the head and neck area (Tardieu spots).
- Tenderness over the larynx may be present and indicates laryngeal fracture.

Investigations

- Routine tests.
- ABG analysis.
- X-ray of cervical spine, anteroposterior and lateral view. It may show fracture of cervical spine. X-ray should be taken after stabilizing the neck with hard collar.
- Chest X-ray.
- CT or MRI of cervical spine provides details of spine and spinal cord injury.

Management

Pre-hospital Care

- C-spine stabilization and airway assessment are of paramount importance.
- Avoid endotracheal intubation in the field unless the airway is acutely compromised in view of possible C-spine fracture. Intubation is indicated if respiratory failure or airway obstruction is present.

In the Hospital

- Take care of airway and breathing. Endotracheal intubation and ventilator support is given for respiratory failure after ruling out C-spine injury. Cricothyroidotomy is performed if endotracheal intubation fails.
- Monitor the patient for cardiac arrhythmias.
- Mannitol is used to treat cerebral edema.
- Phenytoin is given IV to prevent hanging-induced seizures.
- Methylprednisolone 30 mg/kg IV bolus followed by infusion at a dose of 5.4 mg/kg/hr for next 23 hours is given if there is spinal cord injury, because it has been shown to prevent secondary cord damage due to edema and inflammation and improve final functional outcome.

Q. Electric shock/lightening injury.

- Electric current is two types; alternating and direct current. Alternating current is more dangerous than direct current as the former can cause tetanic spasms which hook the victim to the source of current.
- Electrical injuries are almost always accidental and generally preventable.

Mechanism of Injury

- Injuries due to electricity occur by three mechanisms: (1) Direct effect of electrical current on body tissues; (2) Conversion of electrical energy to thermal energy, resulting in deep and superficial burns; and (3) Blunt mechanical injury from lightning strike, muscle contraction, or as a complication of a fall after electrocution.

- The major determinant of injury is the amount of current flowing through the body. In addition, the type and extent of injury also depend on the voltage, resistance, type of current (AC or DC), the current pathway, and duration of contact. Voltage as low as 50 V can be dangerous. Higher the voltage more the danger of cardiopulmonary arrest. Injuries can be generally divided into high voltage (>1000 V) and low voltage (<1000 V) injuries. Voltage in high-tension power lines is greater than 100,000 V, while domestic voltage is 110–220 V. Lightning strikes have a voltage of >10 million V.
- Tissues with higher resistance have a tendency to heat up and coagulate, rather than transmit electric current. Skin, bone, and fat have high resistances, while nerves and blood vessels have lower resistances.
- DC current tends to cause a single muscle spasm that throws the victim from the source. This results in a shorter duration of exposure, but a higher likelihood of associated trauma. In contrast, AC repetitively stimulates muscle contraction. Often, the site of exposure is at the hand and, because the flexors of the arm are stronger than the extensors, the victim may actually grasp the source, prolonging the duration of contact and perpetuating tissue injury.

Clinical Features

- If the current passes through the heart or brainstem, death may be immediate due to ventricular fibrillation, asystole, or apnea.
- *CVS*: Cardiopulmonary arrest can be caused by low-voltage electric injury but is more common with high-voltage electric injury. Various cardiac arrhythmias can occur immediately or later and patients should undergo continuous ECG monitoring for at least 48 hours after electric injury. Vascular injury can result from a compartment syndrome or the electrical coagulation of small blood vessels.
- *Skin and internal organ burns*: Superficial, partial thickness, and full thickness thermal burns can occur following electrical injury. Burns occur due to exposure to electrical arc, clothes catching fire and the heating effect of electricity. Deep burns in the internal organs can occur along the path of current flow. Seemingly minor surface burns may coexist with massive muscle coagulation and necrosis as well as internal organ injury.
- *Nervous system*: Damage to both the central and peripheral nervous systems can occur after electrical injury. Manifestations include loss of consciousness, weakness or paralysis, respiratory depression, autonomic dysfunction, and memory disturbances. Current traversing peripheral nerves can cause acute or delayed neuropathy.
- *Renal*: Myoglobinuria due to rhabdomyolysis may lead to renal failure. Hypovolemia due to extravascular extravasation of fluid can also lead to prerenal azotemia and acute tubular necrosis.
- *GIT*: Direct liver injury, focal pancreatic and gallbladder necrosis, and intestinal perforation have been reported, but are rare. Intestinal perforation may lead to infection, sepsis, and death.
- *Musculoskeletal*: Rhabdomyolysis is common after electrical injuries. It may lead to hyperkalemia, myoglobinuria and renal failure. Damaged muscles may swell and lead to compartment syndrome which may require fasciotomy. Since, bone has the highest resistance to electricity, it generates large amount of heat, resulting in periosteal burns, destruction of bone matrix, and osteonecrosis. In addition, bones can fracture from falls, blast injuries, or repetitive tetanic muscle contractions.
- *Eye*: Cataracts, hyphema, and vitreous hemorrhage may occur.
- *Ears*: Ruptured eardrums, sensorineural hearing loss, tinnitus, vertigo, and injury to the facial nerve may occur especially after lightening strike.

Investigations

- Cardiac monitoring and ECG.
- Complete blood count.
- Electrolytes.
- Renal function tests, LFT.
- Serum CK, and CK-MB.
- Urinalysis, urine myoglobin.

Treatment

- Immediate removal of the patient from the electrical source. The rescuer must be protected. Turn off the power, sever the wire with a dry wooden-handled axe, or separate the victim using nonconductive objects such as dry clothing.
- Cardiopulmonary resuscitation.
- All patients who have shown arrhythmias must undergo ECG monitoring in an ICU for 48 hours.
- IV fluids are required if there are extensive burns and wounds. If there is myoglobinuria, urine output should be maintained at more than 100 ml/hour to minimize intratubular cast formation and renal failure.
- Burns are treated in a similar manner to other thermal burns. Patients may require transfer to a burn unit, fasciotomy, escharotomy, and extensive skin reconstruction.
- Deep tissue damage due to high-voltage injury calls for surgical exploration for assessment of muscle function, and debridement of necrotic tissues to reduce the risk of infection and hyperkalemia. Extensive damage to

muscles, nerves, tendons and vessels may call for amputation at a suitable level.
- If there is any evidence of injury to the abdominal organs, exploratory laparotomy may be required.
- Ophthalmologic examination is required to detect development of cataracts, particularly following lightning injury. Cataracts generally develop several days after injury.
- Physical therapy to maintain functional status.
- Psychiatric consultation for any behavioral disturbances or post-traumatic stress disorder.

Q. High altitude illness.

Q. Acute mountain sickness.

- Exposure to high altitude occurs during air travel and mountaineering. The barometric pressure falls as altitude increases. As a result, the higher one climbs, the lower the barometric pressure and the partial pressure of ambient oxygen. For example, on the summit of Mount Everest, barometric pressure is 253 mm Hg and the ambient oxygen tension is only 53 mm Hg. Reduction in oxygen tension results in a fall in arterial oxygen saturation. Acclimatization to hypoxemia at high altitude involves a shift in this dissociation curve (dependent on 2,3-DPG), erythropoiesis, polycythemia, and hyperventilation due to hypoxia. These changes take a few days to occur.
- Ascent to altitudes up to 2500 meters or travel in a pressurized aircraft cabin is harmless to healthy people. Above 2500 m high-altitude illnesses may occur in healthy people, and above 3500 m they become common.
- Illnesses occurring at high altitude include the following:
  - Acute mountain sickness.
  - High altitude periodic breathing of sleep.
  - High altitude pulmonary edema.
  - High altitude cerebral edema.
  - High altitude retinal hemorrhage.
- In addition to the above, sudden ascent to altitudes above 6000 m may result in decompression illness with the same clinical features as seen in divers. Rapid ascent to altitudes above 7000 m may result in loss of consciousness.

Acute Mountain Sickness (AMS)

Cause

- Hypoxemia at high altitude increases cerebral blood flow and hence intracranial pressure. Cerebral edema occurs in severe cases.

Clinical Features

- Symptoms occur within 6–12 hours of an ascent.
- Symptoms include headache, fatigue, anorexia, nausea and vomiting, difficulty sleeping and dizziness. Ataxia and peripheral edema may also occur.

Treatment

- Most effective treatment is descent to a lower altitude.
- For mild cases, rest and simple analgesia are enough.
- For severe cases, acetazolamide, a carbonic anhydrase inhibitor can be used. It induces metabolic acidosis and stimulates ventilation leading to CO_2 wash out, which causes cerebral vasoconstriction and decreases intracranial pressure. Corticosteroids, diuretics and mannitol are also useful to decrease raised intracranial pressure.
- Acetazolamide may also be used as prophylaxis if a rapid ascent is planned.

Q. Low altitude illness/decompression sickness (caisson disease).

- Decompression sickness occurs when rapid pressure reduction (e.g. during ascent from a dive, exit from a caisson or hyperbaric chamber, or ascent to altitude) causes gas previously dissolved in blood or tissues to form bubbles and cause organ dysfunction.
- Decompression sickness is commonly seen among scuba divers. Ambient pressure under water increases by 1 atmosphere for every 10 meters of seawater depth. As the diver descends and breathes air under increased pressure, the tissues become loaded with increased quantities of nitrogen. As the diver ascends to the surface, there is liberation of free nitrogen gas from the tissues in the form of bubbles. The liberated gas bubbles can cause organ dysfunction by blocking blood vessels, rupturing or compressing tissue, or activating clotting and inflammatory cascades.

Clinical Features

- Symptoms usually occur during or within 4 hours of a dive.
- *General*—tender lymph nodes, edema, headache, nausea, vomiting, fatigue, general malaise.
- *Musculoskeletal*—osteonecrosis, pain in joints due to gas bubble formation.
- *Nervous system*—confusion, visual disturbances, weakness, paralysis, dizziness, paresthesias, aphasia, and coma.
- *RS*—gas embolism may lead to chest pain, cough, hemoptysis, dyspnea.
- *Skin*—itching, erythematous rash.
- *Audiovestibular*—ear and sinus barotrauma may lead to deafness, vertigo, tinnitus, nystagmus.

Management

- Patient is kept in horizontal position.
- Continuous administration of 100% oxygen or hyperbaric oxygen if available. This increases the washout of excess inert gas (nitrogen) and reduces tissue hypoxia due to gas embolism.
- Recompression, in a recompression chamber facility as soon as possible.
- IV fluids to correct the intravascular fluid loss from endothelial bubble injury and the dehydration associated with immersion.
- NSAIDs may be given for pain, but narcotics should be avoided.

Q. Bioterrorism.

- Bioterrorism is terrorism by intentional release or dissemination of biological (bacteria, viruses, or toxins) or chemical agents. These agents may be in a naturally-occurring or in a human-modified form.
- Biological agents can be spread through the air, water, food or objects. Terrorists may use biological agents because they can be extremely difficult to detect and do not cause illness for several hours to several days.
- Bioterrorism is an attractive weapon because biological agents are relatively easy and inexpensive to obtain or produce, can be easily disseminated, and can cause widespread fear and panic beyond the actual physical damage they can cause. However, bioterrorism has some important limitations; it is difficult to employ a bioweapon in a way that only the enemy is affected and not friendly forces.

History of Bioterrorism

- Bioterrorism dates as far back as ancient Roman civilization, where feces was thrown into faces of enemies. In 14th century bubonic plague was used to infiltrate enemy cities. Over time, biological warfare became more complex. Countries began to develop weapons which were much more effective, and much less likely to cause infection to the wrong party.
- In World War I poisonous mustard gas became the biological weapon of choice. Germany used cultures of glanders, a virulent disease of horses and mules to infect French cavalry horses and many of Russia's mules and horses. These actions hindered artillery and troop movements, as well as supply convoys.
- Recently anthrax became a weapon of choice because it is easily transferred, has a high mortality rate, and could be easily obtained. In 1993, a religious group Aum Shinrikyo released Anthrax in Tokyo. The attack was a total failure, infecting not a single person. In 2001 anthrax attacks, several cases of anthrax broke out in the United States. Letters laced with infectious anthrax were delivered to news media offices and the US Congress. The letters killed 5. Tests on the anthrax strand used in the attack pointed to a domestic source, possibly from the biological weapons program.

Types of Agents Used in Bioterrorism

Biologic Agents

- Anthrax, smallpox, botulinum toxin, bubonic plague, brucellosis, glanders, *Vibrio cholerae*, viral hemorrhagic fever and tularemia.

Chemical Agents

- Nerve agents (sarin, soman, tabun), arsine, hydrogen cyanide, phosgene, mustard gas, lewisite, etc.

Prevention and Preparedness

- Government agencies which would be called onto respond to a bioterrorism incident would include law enforcement, hazardous materials/decontamination units and emergency medical units.
- Medical profession must maintain a high index of suspicion especially when there are unusual clinical presentations or the clustering of cases of a rare disease.
- Many countries are creating specially trained forces to deal with bioterrorism.
- Laboratories are working on advanced detection systems to provide early warning, identify contaminated areas and populations at risk, and to facilitate prompt treatment. Forensic technologies are working on identifying biological agents, their geographical origins and/or their initial son.
- Some of the detection methods are: Tiny electronic chips that would contain living nerve cells to warn of the presence of bacterial toxins (identification of broad range toxins), fiber optic tubes lined with antibodies coupled to light-emitting molecules (identification of specific pathogens, such as anthrax, botulinum, ricin), ultraviolet avalanche photodiodes detect anthrax and other bioterrorism agents in the air.
- In the United States, a Strategic National Stockpile (SNS) has been created by the CDC to provide rapid access to quantities of pharmaceuticals, antidotes, vaccines, and other medical supplies that may be of value in the event of biologic or chemical terrorism.

Management of Bioterrorism

- *Surveillance*: If an attack can be detected early, potential victims can be protected with prophylactic medicines or vaccines, and new cases can receive proper medical

treatment. Enhanced surveillance should include ERs, primary care physicians, laboratories, pharmacists, and emergency response systems.

- *Public health response*: State and local health departments should work along with law enforcement agencies.
- *Confirmation/diagnostic testing*: Confirmation of the etiologic agent is important for planning preventive and treatment plans.
- *Decontamination*: It involves removal of clothing and personal effects, placing all items in plastic bags, and shower using copious quantities of soap and water. These items should be disposed appropriately or kept as evidence in a criminal trial or returned to the owner if the threat is unsubstantiated. Regular soap and water were as effective as antimicrobial soap and 2% chlorhexidine gluconate after contact with *B. anthracis*. For incidents involving possibly contaminated letters, the environment in direct contact with the letter or its contents should be decontaminated with a 0.5% hypochlorite solution.
- *Prophylaxis*: Chemoprophylaxis should be given to all exposed persons if appropriate. Vaccines are useful in control of a smallpox epidemic and prevention of a global pandemic. Post-exposure prophylaxis against anthrax (along with antibiotics), protection of laboratory and health care providers working with these agents are also additional preventive measures.
- *Infection control*: This is done by isolation of infected patients, etc. Patients infected with smallpox require aerosol and contact precautions, while those with pneumonic plague require droplet precautions.
- *Specific treatment*: This involves specific antimicrobial drugs, antitoxins, antidotes and vaccines. If the agent is unknown, symptomatic treatment and treatment of coexisting injuries should follow standard guidelines. If the etiologic agent is known, then specific treatment should be instituted against that agent.
- *Psychological support*: Panic among public should be allayed by assurance and educating the public about disease course and outcome.

18 Emergency Medicine and Critical Care

Q. Shock.

- Shock is defined as multifactorial syndrome resulting in inadequate tissue perfusion and cellular oxygenation affecting multiple organ systems.

- *Hypovolemic shock*: Occurs as a consequence of inadequate circulating volume, as may be seen in hemorrhage)
- *Obstructive shock*: This is caused by extra-cardiac obstruction of blood flow. Examples: Cardiac tamponade, pulmonary embolism, tension pneumothorax.
- *Cardiogenic shock*: This is caused by primary pump failure. Examples: Myocardial infarction, myocarditis, etc.
- *Distributive shock*: This is due to widespread vasodilatation leading to hypotension and maldistribution of blood flow and volume. Examples: Septic shock, anaphylactic shock, and neurogenic shock.
- *Endocrine shock*: This results from hormonal pathology. Examples: Acute adrenal insufficiency and myxedema coma.

The fundamental defect in shock is reduced perfusion of vital tissues. Reduced perfusion leads to tissue hypoxia leading to anaerobic metabolism with increased production of CO_2 and accumulation of lactic acid. Cellular function declines, and if shock persists, irreversible cell damage and death occur.

During shock, both the inflammatory and clotting cascades may be triggered in areas of hypoperfusion. There is widespread endothelial dysfunction with increased capillary permeability leading to leakage of fluid and plasma proteins into the interstitial space. In the GI tract, increased permeability may allow the enteric bacteria to enter into the bloodstream, potentially leading to sepsis or metastatic infection. Inflammatory cascade also releases vasodilator substances such as nitric oxide (NO) leading to vasodilatation and hypotension. BP may be normal in the early stages of shock (although hypotension eventually occurs if shock is not reversed).

- In septic shock, blood flow to microvessels including capillaries is reduced due to fibrin deposition even though large-vessel blood flow is preserved.
- Compensatory measures occur to counteract tissue hypoxia and hypotension. Cells extract more oxygen from the blood and there is sympathetic system activation due to hypotension leading to tachycardia and peripheral vasoconstriction. There is selective vasoconstriction (splanchnic circulation, skin) shunting blood to vital organs such as heart and brain.
- Ultimately, because of all these changes, multiple organ dysfunction syndrome (MODS) which is defined as the progressive dysfunction of ≥2 organs sets in leading to death.

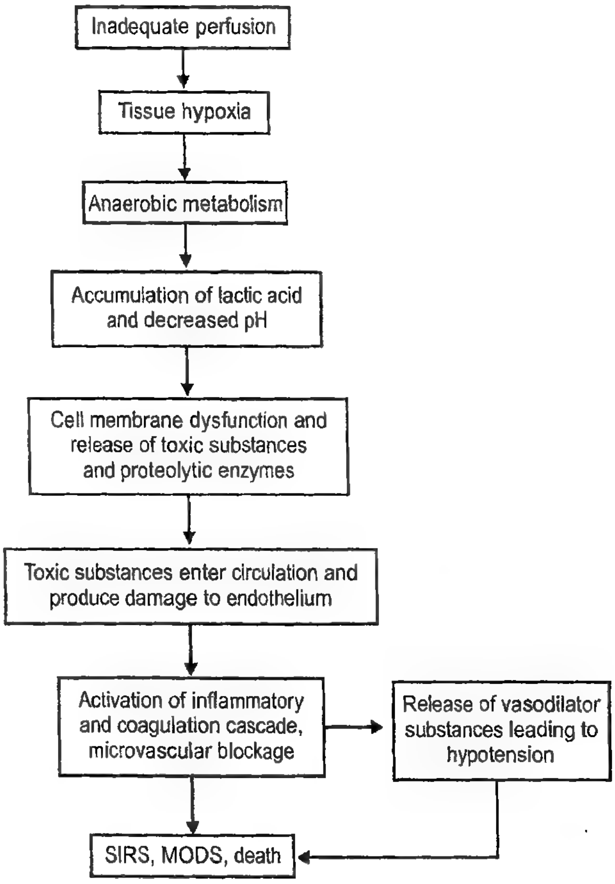

Fig. 18.1: Pathophysiology of shock

Clinical Features

- Lethargy, confusion, and somnolence are common.
- The hands and feet are pale, cool, and clammy.
- Cyanosis may be present.
- Capillary filling time is prolonged.
- Peripheral pulses are weak, tachypnea and tachycardia may be present.
- BP is low (<90 mm Hg systolic) or not recordable. However, it may be normal in early stages of shock.
- In septic shock, skin may be warm, or fever may be present. Some patients with anaphylactic shock have urticaria or wheezing.
- Chest pain and dyspnea may be present in cardiogenic shock due to myocardial infarction.
- Evidence of multiple organ dysfunction syndrome (MODS) such as decreased urine output (kidney involvement), jaundice (liver involvement), dyspnea (ARDS), etc. may be present.

Investigations

- Complete blood count
- LFT and RFT
- Serum electrolytes
- PT and aPTT
- Serum cortisol (if suspecting adrenal insufficiency)
- ABG
- ECG and echocardiogram
- Monitoring of central venous pressure (CVP)
- Chest X-ray and ultrasound abdomen to identify any chest (pneumonia and ARDS) or abdominal pathology.

Treatment

- Admit the patient in ICU and monitor vital parameters.
- Supplemental oxygen by face mask.
- Intubation and mechanical ventilation if shock is severe or if ventilation is inadequate.
- *Intravenous fluids*: Initially 1 liter of 0.9% saline is infused over 15 mins. Further fluid therapy is based on the underlying condition and may require monitoring of CVP.
- If BP remains low even after giving fluid challenge, intravenous infusion of noradrenaline or dopamine is started. Dobutamine is preffered in cardiogenic shock.
- Cardiogenic shock is treated by percutaneous coronary interventions, intra-aortic balloon pump, etc.
- Parenteral antibiotics (meropenem or piperacillin tazobactum) are started if there is supicion of septic shock.
- Intravenous steroids (hydrocortisone or dexamethasone) are given for adrenal insufficiency.

Q. Define systemic inflammatory response syndrome (SIRS). Discuss the etiology, pathogenesis and management of SIRS.

- SIRS is a widespread inflammatory response to a variety of severe clinical insults. SIRS is defined by the presence of ≥2 of the following conditions:
- Fever (oral temperature >38°C) or hypothermia (<36°C).
- Tachypnea (>20 breaths/min) or arterial carbon dioxide tension ($paCO_2$) of less than 32 mm Hg.
- Tachycardia (>90 beats/min).
- Leukocytosis (>12,000/µl), or leukopenia (<4,000/µl), or >10% bands in peripheral blood.
- The etiology of SIRS may be infectious or noninfectious. SIRS that has a proven or suspected microbial etiology is referred to as 'sepsis'.

Causes of SIRS

Infectious (any microbial infection)
- Pneumonia
- Urinary tract infections
- Cellulitis
- Intra-abdominal infections
- Meningitis
- Diabetic foot infection
- Erysipelas
- Infective endocarditis
- Influenza
- Candidiasis

Non-infectious
- Burns
- Trauma
- Drug reaction
- Electrical injuries
- Myocardial infarction
- Pancreatitis
- Seizure
- Extensive surgical procedures
- Transfusion reactions

Pathogenesis

- Basically microorganisms themselves and their products or the noninfectious insult cause activation of inflammatory cells such as macrophages, monocytes, neutrophils, etc. in the host. Activated inflammatory cells release immune mediators called cytokines such as IL-1, IL-6, IL-8 and TNF-α).Other cytokines that have a supposed role in sepsis are IL-10, interferon gamma, IL-12, macrophage migration inhibition factor (MIF), granulocyte colony-stimulating factor (G-CSF), and granulocyte macrophage colony-stimulating factor (GM-CSF). The release of all these cytokines lead to a systemic

inflammatory response syndrome (SIRS) in the host characterized by diffuse endothelial damage, increased vascular permeability, vasodilation, and activation of coagulation cascade.

- Endothelial damage leads to increased capillary permeability leading to intravascular fluid loss and hypotension. Arterial vasodilation is another important cause of hypotension. Cause of vasodilation is multifactorial, but the primary factors are activation of ATP-sensitive potassium channels in vascular smooth muscle and activation of NO synthase. Initially counter-regulatory mechanisms like sympathetic over activity maintain BP but when these mechanisms fail, BP falls and septic shock develops.
- Septic shock is characterized by hypotension (systolic BP less than 90 mm Hg), which leads to tissue hypoxia, which in turn, leads to anaerobic metabolism and increased production of lactic acid. Increased lactic acid leads to metabolic acidosis. Metabolic acidosis leads to tachypnea to allow respiratory compensation. Hypotension also causes decreased renal perfusion which leads to decreased urine output.
- The organism responsible for sepsis may directly affect all the organs like liver, brain, blood, etc. Disseminated intravascular coagulation (DIC) may develop in severe sepsis due to altered regulation of clotting mechanisms.
- A combination of direct affection, hypotension and DIC lead to multiple organ dysfunction as evidenced by bleeding (affection of blood), jaundice (affection of liver), decreased urine output (affection of kidney), altered mental status (affection of CNS), ARDS (affection of lungs). 1 in 2 persons with multiorgan dysfunction and DIC die.

Clinical Features, Investigations and Management

- See under sepsis.

Q. Define bacteremia, sepsis, severe sepsis and septic shock.

Q. Discuss the etiopathogenesis of sepsis. How do you investigate and manage a case of sepsis?

Definition

- *Bacteremia* means the presence of bacteria in the blood.
- *Sepsis* means SIRS that has a proven or suspected microbial etiology.
- *Severe sepsis* is sepsis with dysfunction of one or more organ systems (e.g. hypoxemia, oliguria, lactic acidosis, thrombocytopenia, decreased Glasgow Coma Score).
- *Septic shock* is sepsis with hypotension (arterial blood pressure <90 mm Hg systolic, or reduction of more than 40 mm Hg from baseline) in the absence of other causes of hypotension. Hypotension is not corrected by fluid resuscitation.

Etiology

- Sepsis may be due to any microorganisms like bacteria, virus, fungus, protozoa or rickettsiae. But majority of sepsis cases are due to gram-negative and gram-positive bacteria.

Pathogenesis

- Same as that described under SIRS.

Clinical Features

History

- Fever or hypothermia.
- Tachypnea.
- Decreased urine output.
- Nausea, vomiting, diarrhea.
- Disorientation and confusion.

Examination

General Examination

- Patient may be confused and disoriented.
- Presence of tachycardia, tachypnea and hypotension.
- Temperature high or rarely low (oral temperature >38°C or <36°C, respectively) (low temperature may be seen in neonates, elderly patients, uremic patients, alcoholic patients and immunocompromised patients.
- Pallor and jaundice may be present.
- Peripheries may be cold and cyanosed.
- Cellulitis, pustules, bullae/hemorrhagic lesions may be there. These findings may be the cause or effect of sepsis.
- Petechiae or purpura may be seen in meningococcal infection and Rocky Mountain spotted fever.

RS

- Features of pneumonia and/or ARDS may be there.

CVS

- Features of myocardial dysfunction may be present due to myocarditis such as S3, S4, dilated heart, etc.

Abdomen

- Paralytic ileus, hepatomegaly, splenomegaly.

CNS

- Encephalopathy, especially in elderly patients or those with prior neurologic impairment.

Investigations

- *Complete blood count (CBC)*: It shows leukocytosis (WBC count >12,000/µl) or leukopenia (WBC count <4000) or normal WBC count with >10% immature forms. Thrombocytopenia (platelet count, <100,000/µl) may be present and may indicate direct effect of infections such as dengue or may indicate DIC.
- *Blood cultures*: Send at least two blood cultures from different sites preferably before administration of antibiotics. Culture of other specimens as clinically indicated. For example, urine culture in suspected urosepsis or CSF culture in suspected meningitis.
- *Markers of inflammation*: Elevation of C-reactive protein (CRP) and procalcitonin.
- *RFT*: Elevation of urea and creatinine.
- *LFT*: Elevation of bilirubin, AST, ALT and ALP.
- *Coagulation abnormalities*: INR >1.5 or aPTT >60 secs.
- *Arterial blood gases (ABG)*: It shows hypoxemia and usually metabolic acidosis.
- *Serum lactate*: Elevated due to hypotension, tissue hypoxia and anaerobic metabolism.
- *Procalcitonin*: Elevated serum procalcitonin level is seen in sepsis. This test can be used to differentiate sepsis from SIRS.
- *Chest X-ray*: It may show presence of pneumonia, empyema (which may be cause of sepsis) or ARDS due to sepsis.
- *Echocardiogram*: It can rule out infective endocarditis as a cause of sepsis and may also show myocardial dysfunction in the form of poor ejection fraction.
- *Imaging studies*: Ultrasound or CT scan may be used to identify the source of sepsis in case of localized infections (example, intra-abdominal abscess).
- Other investigations as required to identify the infecting organism such as tests for malaria, WIDAL test, HIV and HBsAg serology, dengue serology, tests for leptospirosis, scrub typhus, etc.

Management of Sepsis and Septic Shock

- The goals are to identify the causative organism, eradicate the focus of infection and pathogens from the blood stream, and correct organ dysfunction.
- Prompt and aggressive treatment is often successful but once septic shock supervenes the mortality is high.

Antibiotics

- Initially a broad spectrum antibiotic is chosen based on the suspected organism and focus of infection. Reasonable initial choice of antibiotics include carbapenems (imipenem, meropenem), or cefoperazone with sulbactam, or piperacillin-tazobactam. Antibiotics can be changed later, once the infecting organism is identified and culture sensitivity reports are available.
- Antibiotics should be administered intravenously.

Supportive Measures

- Intravenous fluids should be administered.
- If the BP is low in spite of giving adequate IV fluids BP should be maintained by giving infusions of noradrenaline or dopamine either alone or in combination. Noradrenaline is the drug of choice in septic shock to maintain BP.
- Respiratory function should be carefully monitored for the development of ARDS and timely intubation and mechanical ventilation instituted where necessary.
- Renal function, hepatic function, and disturbances in coagulation should be assessed and if abnormal managed accordingly. Renal failure may require hemodialysis.
- Deep vein thrombosis (DVT) prophylaxis is required. Use unfractionated heparin (UFH) or low molecular weight heparin (LMWH) unless contraindicated. If heparin is contraindicated, mechanical prophylactic device, such as compression stockings or an intermittent compression device can be used.

Corticosteroids

- Steroids are indicated in septic shock when hypotension responds poorly to fluid resuscitation and vasopressors (noradrenaline). Steroids should not be used in sepsis if hypotension is not present unless the patient's endocrine or corticosteroid history warrants it. Choice of steroid is hydrocortisone (50 mg 6th hourly).

Surgery

- It has a role when there is a well-defined abscess or a foreign body. Wherever there is an abscess it should be drained. Antibiotics alone may be inadequate without draining the abscess.
- Surgery also has a role when the tissues are necrosed and gangrenous and act as a source of infection and sepsis. Such necrosed and gangrenous foci should be removed.

Q. Acute respiratory distress syndrome (ARDS).

Q. Acute lung injury (ALI).

- ARDS was earlier defined as the acute onset of respiratory failure, bilateral infiltrates on chest X-ray, hypoxemia (paO_2/FiO_2 ratio ≤200 mm Hg), and pulmonary capillary pressure <18 mm Hg (if measured) to rule out cardiogenic edema. In addition, acute lung injury (ALI) was defined as paO_2/FiO_2 of 200 to <300 mm Hg.

However, the above definition of ARDS was found to be inadequate and hence, the definition was further refined in 2011 by a panel of experts who met at Berlin and is termed the Berlin definition of ARDS. In the Berlin definition, there is no use of the term acute lung injury (ALI).

ARDS: Berlin Definition

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging (X-ray or CT scan)	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload.
Oxygenation (with PEEP or CPAP ≥5 cm H_2O)	*Mild ARDS*: paO_2/FiO_2 200 to ≤300 mm Hg *Moderate ARDS*: paO_2/FiO_2 100 to ≤200 mm Hg *Severe ARDS*: paO_2/FiO_2 ≤100 mm Hg

Causes of ARDS

- ARDS is caused by diffuse lung injury due to many medical and surgical disorders.

Direct lung injury	Indirect lung injury
Pneumonia	Anaphylaxis (drugs, wasp, bee sting)
Aspiration of gastric contents	Drug overdose (heroin, barbiturates)
Lung contusion	Pancreatitis
Smoke inhalation	Cardiopulmonary bypass
Amniotic fluid embolism	Sepsis
Fat embolism	Shock
Near-drowning	Severe trauma
Diffuse alveolar hemorrhage	Multiple bone fractures
	Multiple blood transfusions
	Burns

Pathogenesis

- Inflammatory cells collect in the lungs because of direct or indirect lung injury listed above. Cytokines are released from inflammatory cells which cause damage to capillary endothelial cells and alveolar epithelial cells. Damage to these cells causes increased vascular permeability and decreased production of surfactant which result in interstitial and alveolar pulmonary edema, alveolar collapse, and hypoxemia.
- Three stages can be recognized in the evolution of ARDS; exudative, proliferative, and fibrotic stages.
- The exudative phase is characterized by alveolar edema, neutrophil-rich leukocytic infiltration and hyaline membrane formation.
- Proliferative phase occurs within 7 days and is characterized by interstitial inflammation and early fibrotic changes. Some patients enter the fibrotic phase approximately 3 weeks after the initial lung injury which is characterized by substantial fibrosis and bullae formation.

Clinical Features

- ARDS is marked by the rapid onset of profound dyspnea that usually occurs 12–48 hours after the initiating event.
- Physical examination reveals labored breathing, tachypnea, intercostal retractions, and diffuse crepitations.
- Many patients with ARDS have multiple organ failure.

Investigations

- *Chest X-ray* shows diffuse or patchy bilateral infiltrates which become confluent with sparing of costophrenic angles. Air bronchograms may be seen. Heart size is normal, and pleural effusions are nil or minimal.
- *ABG* analysis shows marked hypoxemia that is refractory to supplemental oxygen.
- *Bronchoscopy and lung biopsy* can be considered in patients in whom the cause of ARDS is not clear.

Treatment

- Treatment of ARDS must include identification and treatment of the underlying precipitating condition (e.g. sepsis, aspiration, and trauma).
- Treatment of hypoxemia usually requires tracheal intubation and positive-pressure mechanical ventilation. The lowest levels of PEEP (used to recruit atelectatic alveoli) and supplemental oxygen required to maintain the SaO_2 above 90% should be used. Prone positioning may improve oxygenation by recruiting atelectatic alveoli. A variety of mechanical ventilation strategies like using volume-cycled ventilation with small tidal volumes (6 ml/kg of ideal body weight) have shown benefit in trials.
- Fluid administration should be restricted and enough to maintain pulmonary capillary wedge pressure at the lowest level compatible with adequate cardiac output. Crystalloid solutions should be used when intravascular volume expansion is necessary. Diuretics should be used to reduce intravascular volume if pulmonary capillary wedge pressure is elevated.
- Systemic corticosteroids have been studied extensively with variable and inconsistent results. Though steroids cannot be recommended routinely for all patients, studies have shown benefit in late-phase ARDS.
- Supportive care should be provided to minimize venous thromboembolism, gastrointestinal bleeding, and central venous catheter infections. Adequate nutrition should be provided for a good outcome.

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Prognosis

Mortality rate associated with ARDS is 30–40%. Median survival is about 2 weeks.

Most survivors of ARDS are left with some pulmonary symptoms (cough, dyspnea, sputum production), which tend to improve over time.

Q. Respiratory failure.

- Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions, i.e. oxygenation and/or elimination of carbon dioxide. Arterial blood gas criteria for respiratory failure are a paO_2 under 60 mm Hg or a pCO_2 over 50 mm Hg.
- Respiratory failure can arise from an abnormality in any of the components of the respiratory system, including the airways, alveoli, central nervous system (CNS), peripheral nervous system, respiratory muscles, and chest wall.
- Respiratory failure can be classified as follows:
  - *Hypoxemic respiratory failure (type I)*: Hypoxemia present, pCO_2 normal or low. It is caused by processes that impair oxygen transfer in the lung, e.g. acute asthma, pulmonary edema, pulmonary embolism, pneumonia, and ARDS.
  - *Hypercapnic respiratory failure (type II)*: Hypoxemia usually present, pCO_2 high. It is caused by inadequate ventilation leading to retention of CO_2, and hypoxemia, e.g. COPD, myasthenia gravis, brainstem, and stroke.
  - *Mixed respiratory failure*: Here, there is a combination of type I and type II respiratory failure (acute-on-chronic respiratory failure).
- Respiratory failure may be further classified as either acute or chronic. Acute respiratory failure develops over minutes to hours, e.g. pneumothorax, and pulmonary edema. Chronic respiratory failure develops over several days or longer, e.g. COPD.
- Respiratory failure is a serious condition associated with poor prognosis. Incidence and mortality from respiratory failure increase with age and in the presence of other comorbid conditions.
- Prognosis has improved now because of advances in mechanical ventilation and airway management. Even patients with irreversible chronic respiratory failure can now have a reasonably good quality of life with domiciliary ventilator support systems. Lung transplantation is another option for patients with chronic respiratory failure.

Lung disorders
- Asthma
- COPD
- Bronchiolitis
- Obstruction of airways due to mass or foreign body
- Pulmonary edema
- Pneumonia
- Interstitial lung diseases
- Diffuse alveolar hemorrhage syndromes
- Aspiration
- Lung contusion
- Pulmonary embolism
- Pulmonary AV malformations

Muscular disorders
- Botulism
- Neuromuscular blocking agents
- Electrolyte disturbances—hypokalemia, hyperkalemia

Nervous system disorders
- Brainstem disorders
- CNS infections
- Guillain-Barré syndrome
- Myasthenia gravis
- Poliomyelitis
- Spinal cord injury

Chest wall, diaphragm, and pleural disorders
- Rib fracture
- Pneumothorax
- Pleural effusion
- Phrenic nerve injury or dysfunction
- Massive ascites

Drugs
- Sedative overdose
- Anesthetics

Symptoms and signs of acute respiratory failure are those of the underlying disease plus those of hypoxemia and/or hypercapnia.

Dyspnea, cyanosis, restlessness, confusion, anxiety, delirium, tachypnea, hypertension, cardiac arrhythmias, and tremor.

Dyspnea, headache, peripheral flushing, bounding pulses, hypertension, tachycardia, tachypnea, altered sensorium, papilledema, and flapping tremors (asterixis).

Investigations

- *Routine blood tests*: Complete blood count, renal function tests, liver functions tests, and serum electrolytes. Abnormalities in electrolytes such as potassium and magnesium can cause or aggravate respiratory failure.

- *Pulse oximetry* is a noninvasive method to determine arterial oxygen saturation.
- *Arterial blood gas (ABG)* analysis can accurately assess blood oxygen and carbon dioxide content.
- *Chest X-ray* can show any lung pathology such as pneumonia, ARDS, etc.
- *Pulmonary function tests* if feasible.
- *Thyroid function tests* should be done to rule out hypothyroidism as the cause of respiratory failure.
- *Cardiac evaluation* with ECG, echocardiogram, and troponins are important to rule out cardiac problem as a cause of respiratory failure.

Treatment

- Treatment of respiratory failure consists of (1) treatment of underlying disease, (2) respiratory support and (3) general supportive care.
- *Treatment of underlying disease*: Treating pulmonary edema, COPD, myasthenia gravis, etc. which have caused respiratory failure.
- ***Respiratory support***: Providing supplemental oxygen through mask or nasal cannula helps correcting hypoxemia. High concentrations of oxygen are needed for patients with ARDS, pneumonia, and other parenchymal lung diseases. Low flow oxygen should be used in COPD because their respiratory drive may be due to hypoxia. Mechanical ventilator support is required if the patient is not responding to oxygen supplementation. It may be provided via face mask (noninvasive) or through tracheal intubation. Extracorporeal membrane oxygenation (ECMO) is a treatment that uses a pump to circulate blood through an artificial lung and back into the bloodstream. ECMO is indicated in severe respiratory failure not responding to even mechanical ventilation.
- ***General supportive care***: This includes providing adequate hydration and nutrition, preventing stress ulcers in the stomach by using sucralfate syrup, preventing bedsores, and preventing deep vein thrombosis by using subcutaneous heparin or low molecular weight heparin.

Q. Discuss the causes, clinical features and management of hypoxia.

- Hypoxia is defined as lack of oxygen in tissues. Hypoxemia is decreased oxygen concentration of blood. Hypoxia is usually preceded by hypoxemia.

Causes of Hypoxia

- Hypoxia secondary to high altitude.
- Anemic hypoxia.
- Carbon monoxide intoxication.
- Respiratory hypoxia (due to advanced respiratory disease).
- Hypoxia secondary to right-to-left shunting (tetralogy of Fallot, transposition of the great arteries, and Eisenmenger's syndrome).
- Stagnant hypoxia (heart failure, and shock).
- Histotoxic hypoxia (cyanide poisoning).

Clinical Features

- Cyanosis, dyspnea, tachycardia.
- *CNS effects*: Impaired judgment, motor incoordination, fatigue, drowsiness, apathy, inattentiveness, delayed reaction time, and reduced work capacity.
- *CVS*: Pulmonary vasoconstriction, increase in pulmonary vascular resistance and right ventricular afterload. Increase in cardiac output due to generalized vasodilation.
- *Metabolic effects*: Anaerobic metabolism leading to lactic acid production and metabolic acidosis.
- *Blood*: Chronic hypoxia causes secondary polycythemia.

Investigations

- *Pulse oxymetry* may show decreased oxygen saturation.
- ABG (arterial blood gases) shows decreased paO_2 except in histotoxic hypoxia.
- *Chest X-ray*: To rule out any underlying lung disease.
- *Blood tests*: To rule out anemia.
- ECG and echocardiogram to rule out cardiac disorders.

Treatment

- *Oxygen supplementation*: This will correct hypoxia in all cases except in left to right shunts and ventilation perfusion mismatching. Oxygen can be given by nasal cannulae, face mask or through endotracheal intubation.
- Treatment of the underlying cause.

Q. Oxygen therapy.

- Oxygen is widely available and commonly prescribed.
- Oxygen is the vital gas. When administered correctly it is life saving.
- It should be treated like any other drug; it should be prescribed in writing, with the required flow rate and the method of delivery clearly specified.

Indications for Oxygen Therapy

- Cardiac and respiratory arrest.
- Hypoxemia (paO_2 <60 mm Hg, SPO_2 <90%).
- Hypotension (systolic blood pressure <80 mm Hg).
- Low cardiac output and metabolic acidosis (bicarbonate <18 mmol/L).
- Respiratory distress (respiratory rate >24/min).

- *High dose oxygen therapy*: 60–100% oxygen, e.g. asthma, pulmonary embolism, MI, cardiac arrest, respiratory arrest, hypotension, etc. When high-flow masks are used for prolonged periods, oxygen should be humidified by passing it over warm water.
- Low dose oxygen is given to patients with COPD.

Recognizing Hypoxia

- Tissue hypoxia occurs within 4 minutes of stoppage of oxygen supply.
- Successful treatment of tissue hypoxia requires early recognition.
- Clinical features are often non-specific and include altered mental state, dyspnea, cyanosis, tachypnea, arrhythmias, and coma.
- Arterial oxygen saturation (SPO_2) and paO_2 are easily measured and are the main indicators for starting oxygen therapy. However, paO_2 and SPO_2 can be normal when tissue hypoxia is caused by low output cardiac states, anemia, and failure of tissue to use oxygen.

How to give Oxygen?

Oxygen Masks

- The mask and valve design allows delivery of an inspired oxygen of 24 to 90%.
- There are two basic types of oxygen masks. High flow mask and low flow mask. High flow masks contain Venturi valves, which use the principle of jet mixing (Bernoulli effect). When oxygen passes through a narrow orifice it produces a high velocity stream that draws a constant proportion of room air through the base of the Venturi valve. Air entrainment depends on the velocity of the jet (the size of orifice and oxygen flow rate) and the size of the valve ports. It can be accurately controlled to give inspired oxygen levels of 24 to 60%.

Nasal Prongs

- These are simple and convenient to use. The FiO_2 depends on the flow rate of oxygen (1–6 liters/min). Nasal prongs prevent rebreathing, are comfortable for long periods, and allow talking and eating.

Non-invasive Ventilation

- Supplemental oxygen may be provided through tight-fitting nasal or full face masks during nasal intermittent positive pressure ventilation and continuous positive airways pressure.

Invasive Ventilation

- Patient is intubated and endotracheal tube is connected to an oxygen source or a ventilator. Inspired O_2 (FiO_2) can be varied by adjusting ventilator settings.

Monitoring Oxygen Therapy

- *ABG measurements*: ABG analysis provides accurate information on the pH, paO_2, and $paCO_2$, but invasive.
- *Pulse oximetry*: Noninvasive and provides continuous monitoring of the state of oxygenation.

Dangers of Oxygen Therapy

- *Fire*: Oxygen promotes combustion. Facial burns and deaths of patients who smoke when using oxygen are well documented.
- *Oxygen toxicity*: 100% oxygen is both irritant and toxic if inhaled for more than a few hours. Premature infants develop retrolental fibroplasia and blindness if exposed to excessive concentrations. High concentrations of oxygen (>60%) may damage the alveolar membrane when inhaled for more than 48 hours. Progression to the acute respiratory distress syndrome with high protein alveolar edema and pulmonary radiographic infiltrates is associated with high mortality.
- *Paul-Bert effect*: Breathing hyperbaric oxygen (for example, when diving) can cause severe cerebral vasoconstriction and epileptic fits.

Q. Mechanical ventilation.

- Mechanical ventilation is a method to mechanically assist or replace spontaneous breathing by using a mechanical ventilator.
- Mechanical ventilation can be noninvasive or invasive. In noninvasive method, tracheal intubation is not done and ventilation is provided through a tight-fitting face mask, e.g. NPPV (noninvasive positive pressure ventilation). In invasive ventilation endotracheal intubation or tracheostomy is done and patient is ventilated through these.

Indications

- Bradypnea or apnea with respiratory arrest
- Severe hypercapnia not reversed by appropriate specific therapy
- ARDS
- Severe pneumonia
- COPD with respiratory failure
- Acute severe asthma
- Circulatory failure
- Pulmonary edema
- Coma
- Status epilepticus
- Respiratory muscle paralysis (e.g. Guillain-Barré, poliomyelitis, myasthenia gravis)
- Head injury—to reduce intracranial pressure by hyperventilation
- Brainstem disorders affecting respiratory center

Modes of Ventilation

- There are several modes of mechanical ventilation.
- In CMV (controlled mechanical ventilation), minute ventilation is completely dependent upon the rate and tidal volume set. Respiratory efforts made by the patient do not contribute to minute ventilation. CMV is used in patients who are making no respiratory effort (e.g. spinal cord injury or those who have been subjected to pharmacologic paralysis).
- *AC (assist control)*: Here, the minimal minute ventilation is determined by setting the respiratory rate and tidal volume. The patient can increase the minute ventilation by triggering additional breaths. Each patient-initiated breath receives the set tidal volume from the ventilator.
- IMV (intermittent mandatory ventilation): This is similar to AC in that the minimal minute ventilation is determined by setting the respiratory rate and tidal volume. But in IMV, the additional patient initiated breaths are not supported by ventilator.
- In SIMV (synchronized intermittent mandatory ventilation), patient can breathe on his own in addition to the set number of breaths delivered by ventilator. In addition, ventilator breaths are synchronized with patient's inspiratory efforts.
- In CPAP ventilation (continuous positive airway pressure ventilation) breaths are taken by patient and ventilator provides only pressure support.

Weaning from Mechanical Ventilation

- Weaning is slowly taking off the ventilator support. It is done over a period of hours to days. Mechanical ventilation cannot be stopped suddenly as the patient is adapted to ventilator and may not be able to breathe.
- Weaning should be considered when the underlying cause of respiratory failure has resolved.

Complications of Mechanical Ventilation

- Migration of the tip of the endotracheal tube into a main bronchus can cause atelectasis of the contralateral lung and overdistension of the intubated lung.
- Barotrauma can occur in patients ventilated with high tidal volumes and high pressures. There is rupture of alveoli and small airways due to high pressures. It is manifested by subcutaneous emphysema, pneumomediastinum, pneumothorax, or systemic gas embolism.
- Acute respiratory alkalosis can occur due to hyperventilation.
- Hypotension can occur in patients put on excessive PEEP, because excess intrathoracic pressure prevents venous return to heart and hypotension.
- Tracheal stenosis can occur if endotracheal tube is kept for long time.
- Ventilator-associated pneumonia is another serious complication.

19 Case Scenario Based Discussion

- Case scenario based discussions are very helpful to sharpen your diagnostic and interpreting skills. They are an excellent way of learning medicine. Recently, many UG and PG medical examinations include one or two case scenario based questions. In the following pages, there are many common case scenarios which we commonly encounter in our daily clinical practice.

Q. A 30-year-old man presents with 5 days history of fever, headache and vomiting. Headache is diffuse and severe. Examination shows neck stiffness and Kernig sign is positive. Discuss about the most likely diagnosis in this patient.

- The most likely diagnosis in this patient is acute meningitis most probably pyogenic.
- CSF analysis will confirm the diagnosis in this patient.
- Acute meningitis is a medical emergency. Empiric antibiotic therapy should be started as early as possible. The empirical drug of choice is a combination of third-generation cephalosporin (such as ceftriaxone or cefotaxime) plus vancomycin. Ceftriaxone covers *Streptococcus pneumoniae* (the most common organism causing meningitis in adults) whereas vancomycin covers penicillin resistant *Streptococcus pneumoniae*. Vancomycin can be stopped if *Streptococcus pneumoniae* penicillin sensitive as per culture sensitivity report.
- Complications of this condition include hearing loss, cortical blindness, cranial nerve palsies, stroke, seizures, mental retardation, subdural effusions, hydrocephalus, cerebral atrophy, and sepsis.
- Refer 'acute pyogenic meningitis' for more detailed discussion.

Q. A middle-aged farmer presents with 4 days history of fever and generalized body ache. He has also noticed yellowish discoloration of eyes and oliguria. Examination reveals muscle tenderness.

1. **What is your diagnosis?**
2. **What investigation will you do to confirm the diagnosis?**
3. **How do you treat this patient?**

- The most likely diagnosis is leptospirosis because it presents with prominent myalgia due to muscle involvement, jaundice due to liver involvement and oliguria due to kidney involvement. Leptospirosis is common in certain occupations such as farmers, sewage workers and abattoir workers. This patient is a farmer. Patients may also present with meningoencephalitis and ARDS. Leptospirosis is transmitted via direct contact with the body fluid of an acutely infected animal or by exposure to soil or fresh water contaminated with the urine of an animal that is a chronic carrier.
- Serum IgM leptospira antibody will be positive in the blood. Creatine kinase (CK) levels will be elevated in the blood due to muscle damage. LFT and RFT will also be abnormal in this case. Darkfield microscopy can demonstrate leptospira, but not available in all the labs.
- Oral doxycycline can be used in stable patients. For seriously ill patients intravenous penicillin G is the treatment of choice. Third-generation cephalosporins (cefotaxime and ceftriaxone) are as effective as doxycycline and penicillin.
- Refer 'leptospirosis' in 'infectious diseases' chapter for detailed discussion.

Q. A 30-year-old lady presents with history of breathlessness and wheezing of 2 days duration. She also gives history of similar episodes since childhood usually during spring season. She is not a smoker. Her mother also has similar complaints.

1. **What is your diagnosis? Discuss the etiology, pathogenesis, clinical features and treatment of the same.**

- Most likely diagnosis is acute exacerbation of asthma because of similar episodes in the past with seasonal exacerbation, positive family history and onset since childhood. She is also a non-smoker (COPD has to be considered in chronic smokers). All these points favor the diagnosis of asthma.
- Other possibilities to be considered when a patient presents with acute onset breathlessness with wheezing are acute pulmonary edema due to left ventricular failure, acute exacerbation of COPD, allergic reactions causing bronchospasm, tropical pulmonary eosinophilia, eosinophilic pneumonias, etc. Acute bronchitis needs to be considered for a single isolated episode of wheezing. But this patient has recurrent episodes.
- Treatment involves bronchodilators preferably given via nebulizer, i.e. salbutamol nebulization plus ipratropium bromide nebulization 4th to 6th hourly. Nebulized steroids also help in decreasing the severity of attack (e.g. budesonide nebulization every 12th hourly). Oral steroids or parenteral steroids can be given in acute severe asthma. Antibiotics can be given if the cause of asthma exacerbation is respiratory tract infection.
- For a detailed discussion, refer asthma under respiratory system.

Q. A 55-year-old man, who has been smoking for the last 25 years presents with dyspnea on exertion of 8 years duration. Dyspnea has progressed from grade 1 to grade 2 for the last 3 years. He also gives history of recurrent episodes of cough with scanty mucoid sputum associated with wheezing. He does not report any chest pain, orthopnea or paroxysmal nocturnal dyspnea (PND).

1. **What is your diagnosis?**
2. **What findings are you likely to get on examination?**
3. **How do you treat this patient?**

- Most likely diagnosis is COPD, predominantly chronic bronchitis because of chronic cough with wheezing. Other points favoring a diagnosis of COPD are smoking history and progressive breathlessness. It is unlikely to be asthma because asthma does not lead to progressive worsening of breathlessness over the years. It is unlikely to be IHD or heart failure because of the absence of chest pain, orthopnea and PND.
- Other differentials for progressive breathlessness are heart disease (IHD, rheumatic heart disease, cardiac failure), interstitial lung diseases, etc.
- Examination may show barrel-shaped chest, bilateral lung crepitations, and bilateral rhonchi. In advanced COPD, cyanosis, signs of pulmonary HTN such as loud P2, right ventricular hypertrophy (suggested by parasternal heave, shift of apex beat laterally) may be present. Cor pulmonale may develop in advanced cases with significant pulmonary HTN which produces raised JVP with peripheral edema.
- Refer COPD in respiratory system for detailed discussion.

Q. A 40-year-old lady presents with history of recurrent episodes of cough with copious amount of sputum for the past 10 years. She had suffered from pulmonary tuberculosis 15 years ago. Examination reveals presence of clubbing and bilateral basal coarse crepitations.

1. **What is the most likely diagnosis? Discuss the etiology, clinical features, investigations and management of the same.**
2. **How do you prevent recurrent chest infections in her?**

- The most likely diagnosis is bronchiectasis which has developed as a sequelae of past pulmonary tuberculosis. Recurrent episodes of cough with sputum are due to recurrent lower respiratory tract infections.
- Differential diagnosis of chronic cough with bilateral crepitations include extrinsic allergic alveolitis, heart failure, interstitial lung disease, pneumonia and tuberculosis.
- Diagnosis can be confirmed by high resolution CT (HRCT) of chest which will show dilated bronchi. Bronchography can also be done but not commonly done nowadays due to the availability of CT scan.
- Treatment involves antibiotics and chest physiotherapy. Surgery is an option for selected patients with advanced or complicated disease. Antibiotic choices include amoxicillin, doxycycline, trimethoprim-sulfamethoxazole, a newer macrolide (e.g. azithromycin or clarithromycin), cephalosporins or a fluoroquinolone.

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- Recurrent infections can be prevented to some extent by smoking cessation, avoidance of second-hand smoke, good nutrition and immunizations for influenza and pneumococcal pneumonia.
- Refer bronchiectasis in respiratory system for more detailed discussion.

Q. A 50-year-old man presents with cough with expectoration of 2 weeks duration. He says his sputum is of large quantity and foul smelling. Patient says cough and sputum quantity are more on lying in left lateral position. He also gives history of fever.

1. **What is your diagnosis?**
2. **What are the causes of this condition?**
3. **What investigation will you do to confirm the diagnosis?**
4. **How do you treat this patient?**

- Diagnosis is lung abscess in view of large quantity of foul smelling sputum, postural variation of cough and sputum and high grade fever. The abscess is probably in the right lung since the patient gets more cough in left lateral position. In left lateral position right lung is in the upper position and due to gravity the abscess gravity drains into central airways producing more cough and sputum.
- Causes of lung abscess include necrotizing pneumonias due to *Staphylococcus aureus* and *Klebsiella pneumoniae*, tuberculosis, and aspiration pneumonia. Other organisms causing lung abscess are anaerobes such as Peptostreptococcus species, Bacteroides species, Fusobacterium species, and microaerophilic streptococci. Aerobic bacteria that may infrequently cause lung abscess include *Streptococcus pyogenes, Streptococcus pneumoniac* (rarely), *Haemophilus influenzae*, Actinomyces species, Nocardia species, and gram-negative bacilli. A malignant leison can cavitate and produce lung abscess. Non-bacterial pathogens may also cause lung abscesses in the immunocompromised host. These include parasites (e.g. Paragonimus and Entamoeba species), and fungi (e.g. Aspergillus, Cryptococcus, Histoplasma, Blastomyces, and Coccidioides species).
- A chest X-ray will show a cavity with air fluid level. HRCT chest can clearly show the size and extent of an abscess. Microbiological studies of the sputum will identify the microorganism.
- Treatment depends on the presumed infecting organism. For infections caused by anaerobic bacteria, clindamycin (600 mg four times daily IV initially followed by oral dosage of 300 mg four times daily once the patient becomes afebrile and improves clinically) is the drug of choice. Other options are any beta-lactam/beta-lactamase inhibitor combination (example amoxicillin/clavulanate) or carbapenems (e.g. meropenem). Lung abscess due to *S. aureus* is usually treated with vancomycin. Duration of therapy is usually 4 to 6 weeks.
- Refer 'lung abscess' for a detailed discussion.

Q. A 25-year-old man who is a known case of rheumatic heart disease presents with fever of 3 weeks duration. Examination shows petechial hemorrhages, subungual (splinter) hemorrhages, and tender subcutaneous nodules on the digits.

1. **What is the most likely diagnosis?**
2. **What investigation will you do to confirm the diagnosis?**
3. **How do you treat this patient?**

- The most likely diagnosis is infective endocarditis because the patient is a known case of RHD. Tender subcutaneous nodules are Osler nodes. Other signs suggestive of endocarditis should be looked for in this patient such as Janeway lesions (nontender maculae on the palms and soles) and Roth's spots (retinal hemorrhages with small, clear centers). Infective endocarditis can be acute or subacute. Acute infective endocarditis is caused by staphylococcus and Pseudomonas whereas subacute infective endocarditis is caused by *Streptococcus viridans.*
- Though, the obvious possibility is infective endocarditis, simultaneous work up to rule out other causes of fever such as tuberculosis, HIV infection, etc. should be done.
- Duke criteria are used in the diagnosis of infective endocarditis. Presence of two major criteria, or one major and three minor criteria, or five minor criteria is required to make a clinical diagnosis of definite endocarditis. Blood culture and echocardiogram are the most important investigations used to confirm the diagnosis of infective endocarditis and form the major Duke criteria. At least three blood culture sets, ideally with the first separated from the last by at least 1 hour, should be sent from different venipuncture sites over 24 hours.
- Treatment involves empirical antibiotic therapy started as soon as possible after obtaining blood cultures. Empirical therapy should be targeted at the most likely pathogens. Initial choices of antibiotics include benzyl penicillin plus gentamicin. If MRSA is suspected vancomycin should be added. Antibiotics should be given parenteraly.

Q. A 50-year-old chronic smoker presents with retrosternal chest pain on exertion which lasts few minutes and subsides on taking rest. Pain radiates to left shoulder. He also gives history of excessive sweating during episodes of pain.

Discuss the etiology, pathogenesis, clinical features, investigations and management of the most likely diagnosis?

- The most likely diagnosis is stable angina.
- Investigations to confirm the diagnosis include ECG, treadmill testing and coronary angiogram (CAG). Resting ECG can be normal, hence all patients with suspected angina should undergo treadmill testing even if the ECG is normal. CAG can identify which and how much of the coronary artery is blocked.
- Treatment involves nitrates (glyceryl trinitrate, isosorbide dinitrate and mononitrate), beta blockers, antiplatelet agents (aspirin or clopidogrel) and statins (atorvastatin, rosuvastatin). Other useful drugs are ACE inhibitors, non-dihydropyridine calcium channel blockers (diltiazem, verapamil) and nicorandil (potassium-channel activator with a nitrate component). Percutaneous transluminal coronary angioplasty (PTCA) with stenting and coronary artery bypass grafting (CABG) can be used to relieve or bypass the stenotic area. Transmyocardial laser revascularization (TMR) is another new technique where laser is used to make channels (small holes) in the myocardium to allow direct perfusion of the myocardium from blood within the ventricular cavity.
- See 'stable angina' for a detailed discussion.

Q. A 55-year-old diabetic and hypertensive develops severe left-sided chest pain while working. Pain has been present for the last 30 minutes. He also has dyspnea and fatigue. Examination shows diaphoresis, pale cool skin, tachycardia, presence of S3 and bilateral basal lung crepitations.

1. What is your diagnosis?

2. What investigation will you do to confirm the diagnosis?

3. How do you treat this patient?

- The diagnosis is acute myocardial infarction with left ventricular failure (LVF). Chest pain of MI is more severe than angina and lasts for more than 20 minutes (this patient has severe pain and pain is present for 30 minutes). Diaphoresis and tachycardia are due to sympathetic stimulation. Pale cool skin is due to peripheral vasoconstriction due to heart failure and sympathetic stimulation. Presence of S3 and bibasal lung crepitations is due to left ventricular failure and pulmonary edema respectively.
- Investigations to confirm the diagnosis of MI include ECG, CK-MB, troponins and echocardiogram. ECG usually shows ST elevation and formation of pathological Q waves. However, ST elevation may not be present in non-ST elevation MI. Cardiac enzymes such as CK-MB and troponins get elevated after MI. Echocardiogram may show dilated heart and hypokinesia or akinesia of the affected myocardium. Coronary angiogram (CAG)can identify which and how much of the coronary artery is blocked.
- Treatment involves nitrates (glyceryltrinitrate, isosorbide dinitrate and mononitrate), beta blockers, antiplatelet agents (aspirin or clopidogrel) and statins (atorvastatin, rosuvastatin). Other useful drugs are ACE inhibitors, nondihydropyridine calcium channel blockers (diltiazem, verapamil) and nicorandil (potassium-channel activator with a nitrate) component. Percutaneous transluminal coronary angioplasty (PTCA) with stenting and coronary artery bypass grafting (CABG) can be used to relieve or bypass the stenotic coronary arteries. Thrombolysis (using streptokinase or urokinase) can be considered if facility for percutaneous coronary interventions is not available. Transmyocardial laser revascularization (TMR) is another new technique here laser is used to make channels (small holes) in the myocardium to allow direct perfusion of the myocardium from blood within the ventricular cavity.
- See 'myocardial infarction' under CVS chapter for detailed discussion.

Q. A 35-year-old lady presents with easy fatigability and dyspnea on exertion of 4 years duration. She also gives history of recurrent respiratory tract infections. Examination shows hyperdynamic precordium, signs of pulmonary hypertension, widely split and fixed second heart sound.

1. What is your diagnosis?

2. What investigation will you do to confirm the diagnosis?

3. How do you treat this patient?

- The diagnosis is atrial septal defect (ASD). In ASD there is shunting of blood from high pressure left atrium to low pressure right atrium. Consequently, there is increased blood flow into pulmonary circulation.

Increased pulmonary blood flow leads to development of pulmonary HTN. This usually happens above the age of 30 years. Dyspnea and easy fatigability are due to development of pulmonary hypertension. Recurrent respiratory infections are due to increased pulmonary blood flow leading to congestion of pulmonary circulation.

- Echocardiogram and cardiac catheterization can be used to confirm the diagnosis. Echocardiogram shows right ventricular hypertrophy, dilated pulmonary artery, and presence of ASD. Abnormal shunt and blood flow can be assessed by color Doppler. Cardiac catheterization can confirm the presence of ASD but usually echo is enough for confirmation. Cardiac catheterization shows increased oxygen content of right atrial blood due to blood flow from left atrium.
- Surgical closure should be done between 3 and 6 years of age or as soon as possible in significant ASD (i.e. pulmonary flow more than 50% increased compared with systemic flow). Closure should not be carried out in patients with small defects and trivial left-to-right shunts or in those with severe pulmonary hypertension. Angiographic closure is now possible by using a transcatheter device. Infective endocarditis prophylaxis is not required for uncorrected ASDs unless there is another accompanying valvular lesion.
- See '*atrial septal defect*' under CVS chapter for detailed discussion.

Q. A 55-year-old man with history of hypertension presents with sudden onset retrosternal chest pain which is tearing in nature. Examination shows blood pressure of 200/120 and asymmetric peripheral pulses.

Discuss the etiology, pathogenesis, clinical features, investigations and management of the most likely diagnosis.

- This is a case of aortic dissection. Most patients with aortic dissection give history of hypertension. Pain is usually tearing in nature, but it can also be sharp or stabbing in nature. Asymmetry of pulses is a common finding. The DeBakey classification divides the dissections into 3 types. Type I involves the ascending aorta, aortic arch, and descending aorta. Type II is confined to the ascending aorta. Type III is confined to the descending aorta distal to the left subclavian artery.
- Chest X-ray may show mediastinal widening. Echocardiography can identify proximal dissections but not very useful for confirmation of diagnosis. CT or MRI of chest is required for the confirmation of diagnosis.
- Aortic dissection is a life-threatening emergency. Emergency reduction of blood pressure and force of left ventricular contraction is required to halt any further progression of the aortic dissection and to reduce the risk of rupture. Intravenous labetalol is very useful in aortic dissection for controlling hypertension and ventricular contractile force. Intravenous nitroprusside should be added to if BP is not controlled with labetalol. Further treatment depends on the type of dissection. If the dissection involves the ascending aorta, surgical repair is indicated to minimize the risk of life-threatening complications such as blockage of coronary arteries, carotid arteries, etc. If the dissection is confined to the descending aorta, medical therapy is as good as surgical therapy.
- See '*aortic dissection*' under CVS chapter for detailed discussion.

Q. A 25-year-old man presents with 2 months history of diarrhea, low grade fever, and pain abdomen. Stools are watery and contain blood and mucus. Patient has had similar episodes in the past and has recovered without treatment. Examination is normal.

1. **What could be the diagnosis in this case? What are the differential diagnoses?**
2. **How do you confirm the diagnosis?**
3. **How do you treat this patient?**

- The diagnosis in this case could be inflammatory bowel disease (IBD) because of chronic diarrhea, presence of blood and mucus in the stool and recurrent exacerbations and remissions. IBD is of two types; ulcerative colitis and Crohn's disease.
- Other possibilities can be chronic amebiasis, intestinal tuberculosis and AIDS-related infections (*Mycobacterium avium* complex, microsporida, cryptosporidium, *Isospora belli*). Irritable bowel syndrome (IBS) is unlikely because there will not be weight loss and blood in the stool. In addition, IBS will not be associated with fever. Malabsorption syndromes are unlikely again because there will not be fever in these conditions and blood will not be present in the stool.
- Diagnosis can be confirmed by colonoscopy and mucosal biopsy.
- The mainstay of therapy for IBD is 5-ASA (amino salicylic acid) agents. Example is sulfasalazine. Sulfasalazine is not broken down in small intestine and the intact molecule reaches colon where it is broken down by colonic bacteria into sulfa and 5-ASA moieties. 5-

ASA acts as local anti-inflammatory agent in the colon. Newer sulfa-free agents such as mesalamine, olsalazine and balsalazide have less of side effects. Glucocorticoids (prednisolone) can be tried in patients with moderate to severe UC and CD. Immunosuppressive agents (azathioprine, 6-mercaptopurine, methotrexate and cyclosporin) are useful as steroid sparing agents in the management of glucocorticoid-dependent IBD. Tacrolimus and mycophenolate mofetil are newer immunosuppressive agents.

Q. A 30-year-old man who is a chronic alcoholic presents with epigastric pain of 2 days duration after a binge of alcohol intake. Epigastric pain radiates to the back between the scapulae and is associated with nausea and vomiting. Pain worsens on taking food and on lying down. Pain is relieved partially on sitting and bending forward. There is no history of fever or diarrhea.

Discuss the etiology, pathogenesis, clinical features, investigations and management of the most likely diagnosis in this case.

- Diagnosis is acute pancreatitis. It is common in alcoholics and alcohol binge often triggers an attack. Other causes of acute pancreatitis are gallstones, post-ERCP, post-surgical (abdominal, cardiopulmonary bypass), trauma (blunt or penetrating abdominal injury), drugs (azathioprine, thiazides, sulphasalazine, valproate), hypercalcemia, hypertriglyceridemia, infection (mumps, coxsackievirus, HIV, Leptospira, Ascaris), and idiopathic.
- Diagnosis can be confirmed by measuring serum amylase and lipase which will be elevated. Other useful tests are ultrasound abdomen and CT abdomen which can show inflamed and bulky pancreas.
- *Treatment*: Patient should be kept NPO (nil per oral). Ryle's tube aspiration is also required if there is recurrent vomiting. Intravenous fluids are given to maintain intravascular volume. Analgesics are given for to control abdominal pain. Proton-pump inhibitors are used to decrease the acid output. The role of somatostatin or octreotide infusion is controversial.
- Complications of acute pancreatitis include abscess and pseudocyst formation, splenic or portal vein thrombosis, systemic inflammatory response syndrome (SIRS), multiorgan failure, ARDS, and hypocalcemia (due to sequestration of calcium in fat necrosis).

Q. A 20-year-old girl presents with pain abdomen and vomiting of 2 days duration. Initially pain was in the periumbilical region, but later on pain has shifted to right iliac fossa. Examination reveals tachycardia and rebound tenderness in the right iliac fossa at the McBurney's point.

Discuss the clinical features, investigations and management of the most likely diagnosis in this case.

- Diagnosis is acute appendicitis. In acute appendicitis pain is initially felt in the umbilical area (referred pain), but later, it shifts to right iliac fossa due to involvement of peritoneum surrounding the inflamed appendix. Other differential diagnoses are pelvic inflammatory disease (PID) or tubo-ovarian abscess, endometriosis, ovarian cyst or torsion, ureteric colic, diverticulitis, Crohn's disease, and urinary tract infection (UTI).
- Diagnosis can be confirmed by ultrasound abdomen and if required CT abdomen.
- Patient should undergo emergency appendicectomy. Supportive measures include intravenous antibiotics (ceftriaxone and metronidazole), intravenous fluids and analgesics.
- Complications are bowel obstruction, abdominal/pelvic abscess, and, rarely, death.

Q. A 35-year-old man presents with painless, profuse diarrhea of 2 days duration. There is no history of fever or pain abdomen. Stool is watery and appears like rice water. Examination shows moderate dehydration and no other abnormal findings.

1. **What is the possible diagnosis?**
2. **What investigations are helpful to confirm the diagnosis?**
3. **How do you treat this patient?**

- Diagnosis is cholera. Cholera commonly presents as sudden onset, painless diarrhea. Since the causative organism *Vibrio cholerae* does not invade the intestinal mucosa, there is no fever or pain abdomen. Stool appears like 'rice water' because of mucus flecks floating in the watery stools (resemblance to the water in which rice has been washed).
- Other causes of non-invasive watery diarrhea are ETEC (enterotoxigenic *E. coli*), rotavirus, Cryptosporidum, and Girardia.
- Diagnosis of cholera can be confirmed by hanging drop preparation of stool sample (shows rapidly motile organisms) and also by stool culture.

- Mainstay of therapy is oral rehydration salt/solution (ORS). ORS takes advantage of a co-transport mechanism not affected by cholera toxin wherein sodium (Na^+) moves across the gut mucosa along with actively transported glucose. Intravenous fluids may be required if the patient is severely dehydrated or has vomiting. Ringer lactate is the fluid of choice since it contains almost all the electrolytes lost in the stools. Antibiotics can diminish the duration and volume of fluid loss and hasten clearance of the organism from the stool. Single-dose doxycycline (300 mg) is effective in adults but is not recommended for children <8 years of age because of possible deposition in bone and developing teeth.

Q. About 15 people have been brought to emergency department with history of nausea, vomiting, and abdominal cramps. Five of them also have fever and diarrhea. All of them had food at a function of 30 minutes prior to the onset of the above symptoms.

1. What is the possible diagnosis?

2. What investigations would you do?

3. How do you treat them?

- The diagnosis is food poisoning probably due to a preformed toxin produced by Staphylococcus or *Bacillus cereus* since the onset of symptoms after the food intake is within 1 to 6 hours and many are affected at the same time after having the same food.
- Suspected food can be tested for the presence of enterotoxin and Staphylococcus, but usually not necessary.
- Most cases of food poisoning are self-limiting. Intravenous fluids and antiemetics should be given to patients with severe vomiting and diarrhea.
- See 'food poisoning' in 'infectious diseases' chapter for more details.

Q. A 20-year-old lady complains of recurrent episodes of headache since 5 years. She gets 1 to 2 attacks of headache per week lasting 4 to 12 hours. Headache is unilateral and throbbing type and interferes with routine activity. She also reports nausea and vomiting during attacks. Headache worsens on exposure to bright light. There are no other symptoms before or during the headache. Her mother also has similar history of headache.

1. What is the diagnosis?

2. How do you treat her?

- Diagnosis is migraine without aura (also known as common migraine). Migraine with aura is less common and the headache is preceded by transient neurological symptoms such as visual aura (fortification spectra, scotomas), vertigo, speech difficulty, motor weakness, etc. the lady in this case scenario does not have any aura symptoms, hence, it is a case of migraine without aura.
- Migraine is three times more common in females than males and young females are commonly affected. It tends to run in families. Migraine headache is usually unilateral and commonly associated with nausea and/or vomiting. Photophobia (sensitivity to light) and phonophobia (sensitivity to sound) are also common in migraine.
- For an acute attack, paracetamol or any other analgesic can be given along with an antiemetic such as metoclopramide. Triptans (sumatriptan, zolmitriptan) can also abort an attack. Attacks can be prevented by prophylactic drug therapy such as beta blockers (propranolol, atenolol, metoprolol), amitriptyline, verapamil, sodium valproate, and topiramate. Precipitating factors such as certain foods and scents should be avoided.

Q. A 35-year-old man presents with 4 days history of fever, headache, altered mental status, seizures and aphasia. Neck stiffness is absent on examination.

1. What is the likely diagnosis?

2. What are the differential diagnoses?

3. What investigations would you do to confirm the diagnosis?

4. How do you treat him?

- Likely diagnosis is acute encephalitis probably due to herpesvirus. Acute encephalitis typically presents with the above symptoms and speech deficits are common in herpes encephalitis because of involvement of temporal lobe. Absence of neck stiffness argues against meningitis.
- Encephalitis should be differentiated from other causes of altered sensorium such as: Fever with delirium, meningitis with cerebral edema, metabolic encephalopathy, stroke, cerebral venous thrombosis, cerebral abscess, acute disseminated encephalomyelitis (ADEM), and cerebral malaria.
- Diagnosis can be confirmed by CSF analysis which shows a raised WBC count with predominant lymphocytes, normal sugar and mildly elevated protein. CSF-PCR for herpes simplex and other viral serology is helpful to identify the virus. CT and MRI scan may show areas of cerebral edema, often in the temporal lobes. EEG often shows characteristic slow waves.

Treatment of herpes simplex encephalitis is with intravenous acyclovir (10 mg/kg IV q8h) for 10 to 14 days. There is no specific treatment for other viral encephalitis. Supportive treatment involves anticonvulsants, antiedema measures, bedsore prevention, and attention to nutrition through Ryle's tube.

Q. A 40-year-old man presents with 2 days history of progressive bilateral lower limb weakness. Patient says he first noticed weakness in the proximal muscles of lower limbs which has then progressed to involve trunk and upper limbs also. There are no sensory symptoms and there is no history of bowel bladder involvement. Examination shows absent deep tendon reflexes in all 4 limbs and there are no sensory deficits. He also gives history of upper respiratory tract infection 1 week prior to the onset of weakness.

1. What is the diagnosis?
2. What are the differential diagnoses?
3. What investigations would you do to confirm the diagnosis?
4. How do you treat him?

- Diagnosis is acute inflammatory demyelinating polyneuropathy (AIDP) also known as Guillain-Barré syndrome (GBS). The cardinal features of GBS are progressive, symmetric muscle weakness and absent or depressed deep tendon reflexes. Weakness usually starts in the proximal legs, and then ascends up to involve trunk and upper limbs (ascending paralysis). However, in some patients weakness can begin in the arms or facial muscles and then descend down to involve trunk and lower limbs (descending paralysis). Sensory symptoms such as paresthesias occur in the hands and feet in most of the patients, but usually there are no objective sensory deficits. There is often prominent severe pain in the lower back.
- Differential diagnosis includes other causes of symmetric flaccid paralysis such as hypokalemic and hyperkalemic periodic paralysis, tick paralysis and toxin-induced neuropathies. Neurotoxic snakebite and botulism can mimick GB syndrome of descending type where the weakness first starts in bulbar muscles.
- Investigations to confirm the diagnosis are nerve conduction studies (NCS) and electromyography (EMG) which show decreased nerve conduction velocity due to demyelination and decreased amplitude of nerve action potentials due to axonal injury.CSF analysis shows elevated protein with normal WBC count which is known as albuminocytologic dissociation.
- Treatment is by plasmapheresis or intravenous immune globulin (IVIG). Plasmapheresis removes the circulating antibodies and helps in fast recovery. Four sittings of plasmapheresis are recommended. Intravenous immune globulin (IVIG) acts by neutralizing circulating antibodies and immunomodulation. IVIG is given in a dose of 0.4 g/kg daily for 5 days. Both plasmapheresis and IV immunoglobulins have equal efficacy and combining both of them is not better than anyone given alone. Steroids are not effective in GBS.

See 'Guillain-Barré syndrome' in neurology chapter for detailed discussion.

Q. A 30-year-old man presents with 3 days history of bilateral lower limb weakness which developed over a few hours. He says he has decreased sensation below the level of umbilicus. He also has urinary retention for which he has undergone bladder catheterization in a local hospital. He had suffered from an acute febrile illness 1 week prior to the onset of lower limb weakness. Examination reveals a sensory level at the level of umbilicus, increased tone in lower limbs, exaggerated deep tendon reflexes and bilateral extensor plantar response.

1. What is the likely diagnosis?
2. What are the differential diagnoses?
3. What investigations would you do to confirm the diagnosis?
4. How do you treat him?

- Likely diagnosis is transverse myelitis. The term myelitis is a nonspecific term for inflammation of the spinal cord; transverse refers to involvement of complete width of spinal cord. In this case the lesion seems to be at the level of T10, since below this level (level of umbilicus) there is both sensory and motor weakness. Transverse myelitis produces UMN type weakness below the level of lesion which this patient has (as evidenced by exaggerated reflexes, extensor plantars and increased tone in lower limbs). Definite sensory level and bladder involvement also support a diagnosis of transverse myelitis. Causes of transverse myelitis include idiopathic, parainfectious (occurring in association with an acute infection), postvaccinal (rabies, cowpox), autoimmune diseases (e.g. SLE, sarcoidosis), multiple sclerosis, paraneoplastic syndrome and thrombosis of spinal arteries.

Differential diagnosis include other causes of paraparesis/paraplegia such as GB syndrome (LMN type paralysis, absent reflexes, absent sensory level, and no objective sensory deficits), compression of spinal cord (due to tumor, disc prolapse, trauma, epidural abscess), and unpaired ACA territory infarct (absent sensory level, and sensory deficits).

MRI of spinal cord should be done to rule out any alternate pathology (abscess, mass, etc.).

Treatment of idiopathic transverse myelitis is by intravenous steroids (methylprednisolone). Any underlying cause should also be treated.

Q. A 65-year-old man is brought with history of episodes of motionless stare with altered consciousness followed by lip smacking. Each episode lasts 1 to 2 minutes.

1. What is the diagnosis?
2. What investigations would you do confirm the diagnosis?
3. How do you treat him?

- Diagnosis is complex focal seizure. A motionless stare with altered consciousness followed by automatism (e.g. lip smacking, chewing, swallowing) is the usual pattern. Complex focal seizures commonly arise from the temporal lobe.
- EEG usually shows abnormal spikes in the temporal area if done during an attack. MRI brain can pick up any lesion responsible for the seizure.
- Almost all the antiepileptic drugs (AEDs), except ethosuximide are effective in complex focal seizures. Some examples are carbamazepine, phenytoin, sodium valproate, and gabapentin.

Q. A 70-year-old man, who is a known diabetic for the past 30 years is brought with history of [illegible] which recovers fully within one hour. He also gives history of episodes of transient loss of vision in the left eye.

Discuss the clinical features, investigations and management of the most likely diagnosis in this case.

- Diagnosis is transient ischemic attack (TIA). TIA is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (this is the new definition from American Heart Association and American Stroke Association (AHA/ASA) which has eliminated the earlier time limit of 24 hours). This man also has episodes of transient loss of vision in the left eye (amaurosis fugax) indicating left carotid artery disease causing emboli into retinal artery as well as into the brain.

As per definition, brain imaging should not show any infarct. Hence, we expect a normal CT or MRI brain. Cardiac source of emboli should be ruled out by echocardiogram. Four vessels Doppler study of neck (2 vertebral and 2 carotid arteries) can show any stenosis in these vessels which can be further confirmed by angiogram.

- Treatment involves antiplatelet agents (aspirin or clopidogrel) daily lifelong along with lipid lowering agents (statins; atorvastatin, rosuvastatin, etc.). These agents reduce the risk of stroke. Internal carotid endarterectomy is recommended if internal carotid artery stenosis is greater than 70%. Percutaneous transluminal angioplasty (stenting) is an alternative procedure which is being commonly done nowadays.

Q. A 24-year-old man c/o fever, nausea and vomiting of 1 week duration. For the past 2 days, fever has come down but the patient has noticed yellowish discoloration of eyes. There is no history of alcohol or any drug intake. There is no history of clay-colored stools or pain abdomen. His brother also had similar complaints 2 weeks before. Examination shows moderate icterus and tender hepatomegaly.

1. How do you approach this patient?
2. What is the likely diagnosis?
3. What investigations are helpful to confirm the diagnosis?
4. How do you treat him?

- Basically this patient has fever with jaundice. Some important causes of fever with jaundice are acute viral hepatitis, liver abscess, cholecystitis, cholangitis, sepsis, malaria, leptospirosis, dengue, rickettsial fever, etc.
- First possibility to be considered in this patient is acute viral hepatitis. Other causes of acute hepatitis are alcoholic hepatitis, ischemic hepatitis, drug-induced hepatitis, autoimmune hepatitis, and Wilson's disease. This patient does not have history of alcohol or drug ingestion; hence, these are ruled out. Fever is unusual in autoimmune hepatitis and Wilson's disease. Malaria, dengue and leptospira produce multiorgan involvement and fever is a prominent feature. Fever continues along with jaundice. In viral hepatitis, jaundice becomes prominent as the

fever subsides. Hence, this patient most likely has viral hepatitis, though other causes described above have to be ruled out with appropriate investigations.

- Acute viral hepatitis typically presents with fever, nausea and vomiting. Tender hepatomegaly also supports the diagnosis of acute hepatitis. Jaundice appears when fever starts coming down. Absence of clay colored stool and abdominal pain goes against the diagnosis of obstructive jaundice. Hemolytic anemia typically has mild jaundice and pallor also will be present which is not the case here (this patient has moderate icterus). Hemolytic anemia is usually not associated with fever (this patient has fever). Hepatitis A and hepatitis E spreads through food and water and may affect multiple family members. The fact that this patient's brother also had jaundice supports the diagnosis of hepatitis A or E. However, hepatitis B and C also may spread among family members through close contact and have to be ruled out.
- Diagnosis can be confirmed by liver function tests and viral serology. AST and ALT will be usually elevated to above thousand IU. Viral markers such as IgM anti-HAV, HBsAg, anti-HCV, anti-HEV should be sent to identify the specific virus. Appropriate test are done to rule out malaria, dengue, and leptospirosis. Ultrasound abdomen usually shows hepatomegaly and can rule out other causes of jaundice such as cholecystitis, obstruction to biliary tree, liver abscess, etc.
- Acute viral hepatitis is usually self-limited, and treatment is mainly supportive with hydration, vitamins and antipyretics. Hepatoprotective agents such as silymarin and vitamin C are particularly useful. Liver transplantation should be considered for patients who develop fulminant liver failure.

Q. A 35-year-old man who is a known case of cholelithiasis presents with 5 days history of jaundice, right hypochondrial pain, generalized pruritus, and passing clay-colored stool.

1. What is the likely diagnosis?

2. What investigations are helpful to confirm the diagnosis?

3. How do you treat him?

- Diagnosis is obstructive jaundice probably due to a gallstone blocking the common bile duct. Right hypochondrial pain, clay-colored stools and generalized itching all support the diagnosis of obstructive jaundice.
- Ultrasound abdomen is useful to confirm the diagnosis. It may visualize the stone and also show dilated common bile duct. CT abdomen is even more sensitive in picking up the common bile duct stone.
- Endoscopic retrograde cholangiopancreatography (ERCP) can be used to remove stone from common bile duct. If ERCP is not possible, laparotomy and direct removal of stone can be attempted.

Q. A 55-year-old man who is a chronic alcoholic for the past 25 years presents with 10 days history of passing black-colored stools and abdominal distension. Examination shows presence of dilated veins over the abdomen, ascites and moderate splenomegaly. Discuss the pathogenesis, clinical features, investigations and treatment of the most likely diagnosis in this patient.

- Diagnosis is cirrhosis of liver with portal hypertension. Black-colored stool indicates melena due to esophageal varices due to portal hypertension. Presence of ascites, dilated veins over the abdomen and splenomegaly also support the diagnosis of portal hypertension due to cirrhosis. Portal hypertension can also occur without liver disease such as extrahepatic portal hypertension due to portal vein thrombosis, portal vein fibrosis, etc. Here, in this case scenario, there is no mention of features suggestive of liver parenchymal involvement such as jaundice, bleeding tendency, gynecomastia, testicular atrophy, spider nevi, hepatic encephalopathy, etc. These features should be looked for in this patient. Since there is chronic alcohol consumption, probably there is cirrhosis causing portal hypertension.
- Refer 'cirrhosis' in the chapter 'diseases of liver and biliary system' for detailed discussion.

Q. A 52-year-old man who is a known case of cirrhosis of liver presents with 15 days history of jaundice, abdominal distension and right hypochondrial pain. Examination shows irregularly enlarged and tender liver.

1. What is the most likely diagnosis?

2. What investigations are helpful to confirm the diagnosis?

3. How do you treat him?

- Diagnosis is hepatocellular carcinoma which can develop as a complication of cirrhosis of liver. Worsening of liver function, painful irregular enlargement of liver point towards the diagnosis of hepatocellular Ca. Other possibility is acute hepatitis developing in a previously diseased liver due to alcohol binge or viral hepatitis.

Diagnosis can be confirmed by ultrasound abdomen, serum alpha-fetoprotein (AFP) level and biopsy of the lesion. Additional imaging such as CT abdomen may also be required.

- Surgical resection and liver transplantation offers the only chance of cure but is limited by the availability of donors. Local therapies (chemoembolization, ethanol ablation, radiofrequency ablation, cryoablation, and radiotherapy) can be used to reduce the tumor burden. For advanced disease systemic chemotherapy can be tried but response is poor.

Q. A 30-year-old lady presents with 5 months history of easy fatigability and palpitation. She also has history of geophagia and craving for ice. Examination shows presence of pallor, glossitis, angular stomatitis and koilonychia. Discuss the etiology, clinical features, investigations and treatment of the most likely diagnosis.

- Diagnosis is iron deficiency anemia because all the above features are typically seen in iron deficiency.
- Serum iron profile (iron, ferritin, TIBC) is helpful in confirming the diagnosis. Iron and ferritin will be low and TIBC will be elevated. Peripheral smear shows microcytic hypochromic RBCs.
- She should be treated with oral iron supplements. Hemoglobin level will normalize in about 6–8 weeks of iron therapy. However, iron therapy has to be continued for a total of 6 months to ensure repletion of the body iron stores. In addition, any underlying cause of iron deficiency (such as menorrhagia, hemorrhoids, worm infestation, peptic ulcer) should be diagnosed and treated.
- For detailed discussion refer 'iron deficiency anemia' under the chapter 'diseases of blood'.

Q. A 35-year-old lady presents with 5 months history of easy fatigability, tingling and numbness of both feet. She is a pure vegetarian and there is no history of HTN/DM/IHD/asthma or COPD. Examination shows pallor and signs of peripheral neuropathy. Discuss the etiology, clinical features, investigations and treatment of the most likely diagnosis.

- Diagnosis is anemia due to vitamin B_{12} deficiency because she has both anemia and peripheral neuropathy. Fatigability and pallor are due to anemia. Tingling and numbness is due to peripheral neuropathy due to vitamin B_{12} deficiency. Pure vegetarians like this patient are prone to develop vitamin B_{12} deficiency because vitamin B_{12} is found only in foods of animal origin. Vegetarians get their vitamin B_{12} mainly from milk and milk products.
- Diagnosis can be confirmed by measuring serum vitamin B_{12} levels. B_{12} level <200 pg/ml is suggestive of deficiency. Peripheral smear shows macrocytic RBCs and hypersegmented neutrophils.
- Vitamin B_{12} should be replaced by parenteral route since malabsorption is the cause most of the time. 1000 μg should be given intramuscularly per week for 8 weeks, followed by 1000 μg every month for the rest of the patient's life. Oral replacement therapy with 2 mg vitamin B_{12} per day is also effective if malabsorption is not a problem. Any underlying cause of vitamin B_{12} deficiency should be treated (e.g. antibiotics for intestinal bacterial overgrowth, deworming for tapeworm infestation).
- Refer 'vitamin B_{12} deficiency' under the chapter 'diseases of blood' for detailed discussion.

Q. A 25-year-old lady presents with history of feeling tired even with routine physical activity for the last 2 months. She also gives history of passing red-brown urine. Her relatives have noticed yellowish discoloration of her eyes. Examination shows pallor, mild icterus and mild splenomegaly.

1. **What is the most likely diagnosis?**
2. **What investigations are helpful to confirm the diagnosis?**
3. **How do you treat her?**

- Most likely diagnosis is hemolytic anemia in view of presence of tiredness, pallor and jaundice. Red brown urine is due to hemoglobinuria. There are many causes of hemolytic anemia such as hereditary spherocytosis, G6PD deficiency, thalassemias, sickle cell anemia, autoimmune hemolytic anemia, drugs, etc.
- Diagnosis can be confirmed by peripheral blood smear (may show spherocytes, sickle cells, polychromasia, nucleated RBCs), reticulocyte count (increased), Coombs' test (to identify autoimmune hemolytic anemia), and bone marrow examination (shows erythroid, hyperplasia). In addition, there will be indirect hyperbilirubinemia and decreased serum haptoglobin levels. Shortened RBC survival as demonstrated by chromium-51 labeled RBCs.
- Treatment depends on the underlying cause—steroids for autoimmune hemolytic anemia, splenectomy in hereditary spherocytosis and sickle cell anemia, withdrawal of offending drug, etc.

- For detailed discussion refer hemolytic anemia in the chapter 'diseases of blood'.

Q. A 50-year-old man presents with history of easy fatigability and left hypochondral pain. Examination shows pallor and massive splenomegaly. His complete blood count shows Hb of 5 g/dl, WBC count of 1,50,000/cu mm and platelet count of 2,25000/cu mm.

1. What is the most likely diagnosis?

2. What further investigations would you like to do?

3. How do you treat him?

- Most likely diagnosis is chronic myeloid leukemia in view of very high leukocyte count and massive splenomegaly.
- Other causes of massive splenomegaly such as hairy cell leukemia, kala-azar, tropical splenomegaly, etc. should also be considered in this case and ruled out by appropriate investigations.
- Peripheral blood smear shows presence of myelocytes and metamyelocytes. Bone marrow aspiration and biopsy shows myeloid hyperplasia, increase in reticulin fibers and vascularity. There is increase in the myeloid-to-erythroid ratio in the bone marrow. Diagnosis of CML can be confirmed by the demonstration of the Philadelphia chromosome or the BCR-ABL fusion gene. BCR-ABL can be detected in the peripheral blood by polymerase chain reaction (PCR) test, which has now supplanted cytogenetics.
- Conventional treatment of CML in chronic phase has been single agent therapy with busulphan or hydroxyurea. Alpha-interferon is also helpful. Introduction of imatinib mesylate which inhibits the tyrosine kinase activity of the BCR/ABL oncogene has revolutionized the treatment of CML.

Q. A 35-year-old lady c/o multiple joint pain involving bilateral ankle, knee, small joints of hands, wrist, elbow and shoulder since 6 months. Joint pain is worse in the morning and is associated with early morning stiffness.

1. What is the most likely diagnosis?

2. What are the differential diagnoses?

3. What further investigations would you like to do?

4. How do you treat her?

- Most likely diagnosis is rheumatoid arthritis (RA). Characteristic clinical features of RA are as follows:
  - Morning stiffness of at least 1 hour and present for at least six weeks.
  - Swelling of three or more joints for at least six weeks.
  - Arthritis of hand joints.
  - Symmetrical arthritis.
  - Presence of rheumatoid subcutaneous nodules.
  - Positive rheumatoid factors or anti-cyclic citrullinated peptide (anti-CCP) antibodies.
  - Elevated acute phase reactants (erythrocyte sedimentation rate or C-reactive protein).
  - Radiological changes (erosions or unequivocal bony decalcification adjacent to the involved joints.

Differential diagnoses include other diseases which can present with polyarthritis as follows

- Acute viral polyarthritis (such as chickungunya, associated with acute onset polyarthritis, usually transient, subsides without any residual deformities)
- Systemic rheumatic diseases such as SLE, systemic sclerosis.
- Reactive arthritis (usually oligoarthritis involving large joints such as knee, ankle, etc.)
- Lyme arthritis.
- Psoriatic arthritis (usually oligoarthritis.
- Polymyalgia rheumatic (frank arthritis is unusual).
- Crystalline arthritis (e.g. gout. Usually monoarthritis).
- Infectious arthritis (such as tuberculous arthritis, gonococcal arthritis: Usually oligoarthritis involving large joints)
- Osteoarthritis (usually involves large weight bearing joints such as knee, hip, etc. pain worse in the evening, seen in elderly)
- Further investigations which are helpful are rheumatoid factor, anti-CCP antibody, CRP, ESR, ANA (a negative ANA helps to rule out SLE and other systemic rheumatic diseases), hand X-rays to look for joint erosions.
- Treatment involves rest, analgesics, and disease-modifying antirheumatoid drugs (DMARDs which include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide). Methotrexate is given in a dose of 7.5–25 mg per week. Folic acid should be given along with methotrexate to prevent hematological side effect. Hydroxychloroquine is given at a dose of 200–400 mg daily. Steroids are useful as part of combination drug therapy along with NSAIDs and DMARDs during initial control of the disease and during flare ups. Biological agents such as infliximab and rituximab are also useful in refractory disease.

Q. A 30-year-old lady presents with malar rash, photosensitivity, and polyarthralgia of 5 years duration. She also gives history of recurrent abortions and Raynaud's phenomenon. Discuss the etiology, clinical features, investigations and treatment of the most likely diagnosis.

- Most likely diagnosis is systemic lupus erythematosus (SLE). SLE frequently affects women in their 20s and 30s. It affects almost all the organs and usually begins with one or several of the following features such as: Fever, fatigue, malar rash (butterfly rash), arthralgia or arthritis, Raynaud's phenomenon, serositis (pleuritis, pericarditis, peritonitis), nephritis or nephrotic syndrome, seizures, alopecia, recurrent abortions, and anemia.
- Complete blood count shows anemia or pancytopenia. ESR, CRP are elevated and complement levels (C3, and C4) are decreased. Antinuclear antibodies (ANA), antiphospholipid antibodies, antibodies to double-stranded DNA and anti-Smith (Sm) antibodies may be positive. Anti dsDNA and anti-Sm antibodies are highly specific for the diagnosis of SLE.
- Mainstay of treatment is steroids. Immunosuppressive drugs (azathioprine, methotrexate, ciclosporin, tacrolimus, mycophenolate mofetil) are useful either alone or in combination with steroids for severe manifestations. Hydroxychloroquine also is useful for cutaneous and joint symptoms. Lifelong anticoagulation is required for patients with the antiphospholipid antibody syndrome with thrombotic events.
- For detailed discussion refer 'SLE' in Chapter 10 'diseases of immune system, connective tissue and joints'.

Q. A 25-year-old man presents with insidious onset of low back pain and stiffness of 6 months duration. He also has pain in the ankle, knee and hip joints. Examination shows restricted spinal mobility and sacroiliac joint tenderness.

1. What is the most likely diagnosis?

2. What investigations are helpful to confirm the diagnosis?

3. How do you treat him?

- Most likely diagnosis is ankylosing spondylitis. It is a type of seronegative spondyloarthropathy. It mainly affects males and the peak incidence is between 20 and 30 years. Most important feature is involvement of lumbosacral spine with restriction of mobility in all directions. Note that rheumatoid arthritis also involves spine but usually cervical spine. In addition, restriction of spine mobility is unusual in rheumatoid arthritis. Degenerative spine diseases such as spondylosis also involve spine and cause restricted mobility, but occur in old age and also do not affect peripheal joints. Extra-articular features are also common in seronegative spondyloarthropathies and include enthesitis (inflammation at tendon insertion sites), scleritis, uveitis, mucosal ulcers, etc.
- ESR and CRP are elevated. Rheumatoid factor is usually negative. HLA-B27 is usually positive. X-ray of sacroiliac joint shows irregularity and loss of cortical margins, sclerosis, narrowing and fusion. In advanced cases, there will be fusion of vertebras which produces bamboo spine appearance on X-ray.
- Treatment involves both non-pharmacological and pharmacological therapies. Non-pharmacological therapy involves smoking cessation and exercise. Pharmacological therapy involves NSAIDs, DMARDs (sulfasalazine, methotrexate), and TNF-α antagonists (infliximab, etanercept, adalimumab). However, methotrexate has been shown to be of a little use in ankylosing spondylitis.

Q. A 60-year-old lady presents with right temporal headache of 5 days duration. She also has blurring of vision in the right eye. Routine investigations showed that her ESR is 100 mm/hour. Discuss the etiology, clinical features, investigations and treatment of the most likely diagnosis.

- The diagnosis is temporal arteritis. Temporal arteritis is common in elderly (above 50 years of age). It is more common in females. Typical presentation is temporal headache with blurring of vision. There will be tenderness over the temporal artery. ESR is usually high.
- Diagnosis can be confirmed by temporal artery biopsy. Biopsy will show infiltration of temporal artery with lymphocytes, fragmentation of internal elastic lamina and destruction of tunica media.

  Treatment is with steroids. Steroids should be started immediately on suspicion without waiting for confirmation of diagnosis. Dose of prednisolone is 40 to 60 mg per day for 1 to 2 months initially, followed by slow tapering. Typical duration of therapy is 9 to 12 months. Low dose aspirin is also useful to reduce the risk of visual loss, TIA and stroke.
- For detailed discussion refer 'temporal arteritis' in Chapter 10 'diseases of immune system, connective tissue, and joints'.

Q. A 50-year-old man who is a chronic alcoholic presents with confusion and disorientation. Examination shows nystagmus, ophthalmoplegia and ataxia. There are no motor or sensory deficits. CT brain is essentially normal. Discuss the etiology, clinical features, and treatment of the most likely diagnosis.

- Most likely diagnosis is Wernicke's encephalopathy (WE). WE typically occurs in chronic alcoholics due to thiamine deficiency. It should be suspected in any alcoholic presenting with the triad of encephalopathy, ataxia and ophthalmoplegia.
- WE is mainly a clinical diagnosis. Imaging (CT or MRI brain) is useful to rule out alternative diagnosis). Measurement of erythrocyte transketolase activity after adding thiamine pyrophosphate can be used to diagnose thiamine deficiency.
- Patients suspected to have WE should be treated with intravenous thiamine immediately, without waiting for confirmation of diagnosis. Thiamine 500 mg should be given as IV infusion three times daily for 2 days followed by 500 mg once daily IV or IM once daily for 5 days. This is followed by 100 mg daily orally as long as the patient is at risk of developing deficiency. Administration of glucose in the presence of thiamine deficiency can precipitate thiamine deficiency, because thiamine is an important co-enzyme in glucose metabolism (conversion of pyruvate to acetyl CoA). Hence, thiamine should be given before giving glucose.

Q. A 50-year-old chronic alcoholic presents with confusion and memory loss. He also gives history of diarrhea of 3 months duration. Examination shows dark, dry and scaly skin lesions around the neck, hands and legs.

1. **What is the most likely diagnosis?**
2. **What investigations are helpful to confirm the diagnosis?**
3. **How do you treat this patient?**

- Most likely diagnosis is pellagra due to niacin deficiency. Niacin deficency is common in alcoholics, malabsorption disorders and anorexia nervosa. Niacin deficiency can occur in Hartnup's disease which is characterized by defective absoprtion of several amino acids. Similarly niacin deficiency can also occur in carcinoid syndrome where tryptophan is converted to 5-HT and serotonin rather than niacin. Pellagra is characterized by 3 Ds, diarrhea, dementia and dermatitis. This pateint has all these features.
- Pellagra is treated by niacin supplements 100 mg 3 times daily orally or parenterally for 5 days.
- Refer 'pellagra' for more details.

Q. A 30-year-old lady presents with easy fatigability, cold intolerance, and amenorrhea after the last child birth. She had suffered severe postpartum hemorrhage and also lactation failure after last child birth. Examination is otherwise normal except dry skin.

1. **What is the most likely diagnosis?**
2. **What investigations are helpful to confirm the diagnosis?**
3. **How do you treat this patient?**

- Most likely diagnosis is hypopituitarism due to Sheehan's syndrome. Hypopituitarsim due to infarction of the pituitary gland after postpartum hemorrhage is called Sheehan's syndrome. The pituitary gland is physiologically enlarged in pregnancy and is therefore very sensitive to the decreased blood flow caused by massive hemorrhage and hypovolemic shock.
- Failure to lactate or difficulties with lactation are common initial symptoms of Sheehan's syndrome (due to prolactin deficiency). Many women also report amenorrhea or oligomenorrhea after delivery (due to FSH and LH deficiency). Other features include fatigue, anorexia, weight loss (due to decreased ACTH), and features of hypothyroidism (due to decreased THS).
- There is deficiency of all the hormones, i.e. growth hormone, prolactin, gonadotropins, TSH and ACTH. CT scan or MRI shows a small pituitary within a sella of normal size, sometimes read as an "empty sella".
- Treatment of hypopituitarism involves the treatment of each individual target gland hormone deficiencies. ACTH deficiency is treated by giving hydrocortisone or other glucocorticoid. TSH deficiency, which results in thyroxine deficiency, is treated with L-thyroxine.

Q. A 30-year-old woman c/o weight loss, increased appetite, heat intolerance and palpitations since 2 months. Examination shows a pulse rate of 105/minute and fine tremors of hands.

1. **What is your diagnosis?**
2. **How do you confirm the diagnosis?**
3. **How do you treat this patient?**

- Diagnosis is thyrotoxicosis.

- Diagnosis can be confirmed by thyroid function tests. In primary hyperthyroidism, T3, T4 will be elevated and TSH will be suppressed. In central hyperthyroidism, all three will be elevated.
- Treatment involves antithyroid drugs. Methimazole is started at 5 to 10 mg OD and can be increased to 30 to 40 mg per day. Propyl thiouracil (PTU) is given at a dose of 100 to 150 mg every 8 hours. Radioactive iodine (^{131}I) is used to treat hyperthyroidism in older patients but is contraindicated in pregnant ladies. Subtotal thyroidectomy is another option for patients with thyroid enlargement causing obstructive symptoms.
- For more details refer 'hyperthyroidism' in the chapter 'endocrinology and diabetes mellitus'.

Q. A 35-year-old patient presents with weight gain, cold intolerance and hoarseness of voice since 2 months. Examination shows dry skin and bilateral non-pitting pedal edema

1. What is your diagnosis?

2. How do you confirm the diagnosis?

3. How do you treat this patient?

- Diagnosis is hypothyroidism.
- Diagnosis can be confirmed by thyroid function tests. In primary hypothyroidism, T3, T4 will be low and TSH will be elevated. In central hypothyroidism, all three will be low.
- Treatment involves thyroxine supplementation. Thyroxine should be started at a low dose and increased every 6 to 8 weeks till thyroid function is normalized. Initial dose should be low especially in patients with IHD, because high initial dose of thyroxine can precipitate angina and heart failure by increasing BMR.
- For more details refer 'hypothyroidism' in the chapter 'endocrinology and diabetes mellitus'.

Q. A 40-year-old man presents with weight loss, easy fatigability, and darkening (hyperpigmentation) of skin of a few months duration. Examination shows BP of 90/60 mm Hg. Investigations show Na^+ of 130, K^+ of 5.5 and his random blood sugar is 70 mg/dl.

1. What could be the diagnosis?

2. How do you confirm the diagnosis?

3. How do you treat this patient?

- Diagnosis is adrenal insufficiency (Addison's disease). Adrenal insufficiency is of two types: Primary (inability of the adrenals to produce hormones), secondary (due to pituitary or hypothalamic disease leading to ACTH and CRH deficiency). Symptoms and signs are due to low glucocorticoid, low mineralocorticoid, low adrenal androgen levels and secondary increase in ACTH. Glucocorticoid deficiency causes malaise, fatigue, generalized weakness, nausea, vomiting, anorexia, weight loss, postural hypotension with postural drop and hypoglycemia. Mineralocorticoid deficiency causes hyponatremia and hyperkalemia. ACTH excess in primary adrenal deficiency causes hyperpigmentation. Hyperpigmentation is not seen in secondary adrenal insufficiency as ACTH is low.

Investigations

- ***Serum cortisol level*:** An early morning (between 8 to 9 AM) serum cortisol concentration less than 3 μg/dl suggests adrenal insufficiency and a value above 19 μg/dl excludes it.
- ***ACTH stimulation test (synacthen test)*:** 250 mcg ACTH (Synacthen) is given by IM injection at any time of day. Blood samples are drawn at 0 and 30 minutes for plasma cortisol. In normal subjects plasma cortisol is >17 μg/dl either at baseline or at 30 minutes. Cortisol level fails to increase in primary adrenal insufficiency.
- ***ACTH level*:** Primary and secondary adrenal insufficiency can be distinguished by measurement of ACTH which is low in ACTH deficiency and high in Addison's disease.
- Ultrasound abdomen is useful to assess the size of adrenals and also to detect any tumors.
- CT or MRI of adrenals to look for size of adrenals.

Management

Cortisol 15 mg in the morning and 5 mg at 6 pm or prednisolone 5 mg in the morning and 2.5 mg in the evening lifelong. Steroid dose should be doubled during intercurrent illness. Patient should carry a steroid card all the time which should give information regarding diagnosis, steroid dose and the doctor.

Q. A 50-year-old patient presents with polyuria, excessive thirst and increased appetite. He also has weight loss since last [illegible] months and recurrent skin infections.

1. What is your diagnosis?

2. How do you confirm the diagnosis?

3. How do you treat this patient?

- Diagnosis is diabetes mellitus in view of polyuria, polydypsia, polyphagia and recurrent skin infections. The

type of diabetes is probably type 2 DM, because the patient is 50 years old. Type 1 DM is unlikely because it usually occurs in children and young adults. Secondary diabetes due to pancreatic disease is possible and should be ruled out by appropriate investigations. Patients with chronic pancreatitis usually c/o epigastric pain worsened by food intake, and bulky foul smelling stools (steatorrhea).

- Polyuria occurs due to the osmotic diuresis caused by sugar in the urine. Polydypsia occurs secondary to excess loss of fluid in the urine and also due to increased osmolality of blood due to excess sugar. Polyphagia is due to loss of calories in the urine (as glucose) and also the inability of the body to use glucose due to lack of insulin or insulin resistance.
- Diagnosis can be confirmed by doing FBS and PPBS. An FBS of more than 110 mg/dl and a PPBS of more than 200 mg/dl confirms diabetes mellitus.
- Treatment involves diet control, exercise, anti-diabetic drugs and insulin. Anti-diabetic drugs include sulphonylureas, biguanides, glitazones, alpha-glucosidase inhibitors, meglitinides, PPP-4 inhibitors.

Q. A 34-year-old lady who has undergone total thyroidectomy for papillary carcinoma thyroid 2 months ago presents with history of episodes of paresthesias involving fingertips, toes, perioral area and muscle cramps involving low back, legs and feet.

1. What is your diagnosis?
2. How do you confirm the diagnosis?
3. How do you treat this patient?

- Diagnosis is hypoparathyroidism. This patient has undergone total thyroidectomy, hence even the parathyroid glands which are very close to the thyroid glands must have been removed leading to hypoparathyroidism. Paresthesias and muscle cramps are due to hypocalcemia. Other causes of hypoparathyroidism are irradiation of the neck, Type 1 autoimmune polyglandular syndrome, and congenital agenesis or hypoplasia of the parathyroid gland.
- Diagnosis can be confirmed by measuring serum calcium which will be low and serum parathormone (PTH) level which also will be low. Measurement of 25-hydroxy-vitamin D is important to exclude vitamin D deficiency as a cause of hypocalcemia. Serum magnesium level should also be measured as low magnesium also causes symptoms similar to hypocalcemia. In addition, hypomagnesemia may cause PTH deficiency and subsequent hypocalcemia.
- Treatment involves supplementation of vitamin D and calcium. Currently parathormone use is approved for use only in patients with osteoporosis.

Q. A [illegible]-year-old man is brought with 1 month history of altered behavior. He is socially withdrawn, appears depressed, has difficulty in taking care of himself, reports hearing voices, and believes that people are inserting thoughts into his mind. His routine blood tests are normal.

1. What is your diagnosis?
2. How do you treat this patient?

- Diagnosis is schizophrenia.
- Treatment is by antipsychotics such as clozapine, risperidone, olanzapine, and quetiapine.
- For detailed discussion refer 'schizophrenia' in the chapter 'psychiatric disorders'.

Q. A [illegible] year-old [illegible] found unconscious at his house. [illegible] kerosene smell [illegible] with a pulse rate of [illegible] 90/60 mm Hg. There is excess salivation and [illegible] sweating. His pupils are constricted and there are fasciculations also. Discuss the etiology, clinical features, investigations and treatment of the most likely diagnosis in this patient.

- Diagnosis is organophosphorus poisoning. Usually organophosphorus compounds have the smell of kerosene. Clinical features can be divided into 3 phases: Acute cholinergic phase, intermediate syndrome, and organophosphate-induced delayed polyneuropathy (OPIDN). Acute cholinergic phase is characterized by bradycardia, constricted pupils, increased body secretions and fasciculations. Intermediate syndrome starts 1 to 3 days after exposure to poison. It occurs due to receptor dysfunction at the neuromuscular junction and is characterized by weakness of neck muscles, decreased deep tendon reflexes, cranial nerve abnormalities, proximal and respiratory muscle weakness or paralysis. OPIDN occurs about 1–3 weeks after acute OP exposure and is characterized by transient, painful "stocking-glove" paresthesias followed by a symmetrical motor polyneuropathy.
- Diagnosis can be confirmed by history and by measuring plasma cholinesterase levels which will be reduced to less than 50% of normal.

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- Treatment involves gastric lavage, activated charcoal and IV fluids. Antidote is atropine which antagonizes the muscarinic effects of acetylcholine. Atropine does not reverse nicotinic effects such as muscle fasciculation. Initially 2 to 5 mg is given IV. If no effect is noted, the dose is doubled every three to five minutes until the muscarinic signs and symptoms are reversed. Atropine infusion is usually required for several days after the exposure. Intravenous glycopyrrolate is an alternative and does not have many CNS side effects of atropine. Oximes such as pralidoxime (PAM) and obidoxime are cholinesterase reactivating agents and are effective in treating both muscarinic and nicotinic effects of OP compound. Dose of PAM is 2 g IV infusion over 30 minutes. Intermediate syndrome is treated by ventilator support. There is no specific therapy for OPIDN. Regular physiotherapy may reduce deformities and muscle-wasting.
- Refer organophosphorus poisoning for more details.

Q. A 22-year-old student is found unconscious in his room. Examination shows low respiratory rate (10 breaths per minute), pulse rate of 55/min, normal BP, decreased chest movements, decreased bowel sounds and miotic pupils. Discuss the etiology, clinical features, investigations and treatment of the most likely diagnosis in this patient.

- The diagnosis is opioid intoxication. The classic signs of opioid intoxication include: Depressed mental status, decreased respiratory rate, decreased tidal volume, decreased bowel sounds, and constricted pupils. Rarely normal sized pupils can be seen if the patient has taken meperidine or propoxyphene or presence of sympathomimetic or anticholinergic co-ingestants. Constricted pupils can also be seen in organosphosphorus poisoning and pontine hemorrhage. However, absence of kerosene smell, decreased bowel sounds argue against OP poisoning. Pontine hemorrhage can present with similar picture and should be ruled out by CT or MRI brain.
- Diagnosis of opioid poisoning is made clinically. However, diagnosis can be confirmed by response to naloxone which is an opioid antagonist.
- Initial management involves support of patient's airway and breathing. Naloxone (opioid antagonist) is given intravenously, initially 0.05 mg is and the dose is titrated upwards every few minutes till the respiratory rate is 12 or more. Activated charcoal and gastric emptying are usually not necessary and may increase the chances of aspiration in an unconscious patient.

Q. A 44-year-old man presents with history of ingestion of illegal alcohol followed by nausea, vomiting, abdominal pain, and severe watery diarrhea. There is garlic odor of the breath and stool. Discuss about the most likely diagnosis in this patient.

- The diagnosis is acute arsenic poisoning. Arsenic poisoning can occur in people working in industries dealing with semiconductors (gallium arsenide), smelting/refining, mining, metallurgy, and decorative glass-making. It can also occur after ingestion of arsenic-containing pesticides, herbicides and some "moonshine" (illegally distilled alcohol). Symptoms start in the gastrointestinal system and include nausea, vomiting, abdominal pain, and watery diarrhea which can lead to dehydration and hypotension. Garlic odor of breath and stool is typically found in severe poisoning. Other features are cardiac arrhythmias, shock, ARDS, acute encephalopathy, and sometimes death.
- Another consideration is methanol poisoning. But it is associated with blurring of vision or blindness, features of metabolic acidosis, etc.
- Diagnosis of arsenic poisoning can be established by taking an X-ray of the abdomen which may show radiopaque material soon after ingestion. ECG may show QT prolongation. Blood arsenic level are usually raised but since blood arsenic is cleared rapidly, measurement of urine arsenic levels can confirm the diagnosis. In acute poisoning, urine arsenic levels are usually in the thousands of micrograms per liter.
- Initial treatment should concentrate on stabilizing the patient in terms of airway, breathing and circulation. Gastric lavage and activated charcoal is given if the ingestion has been recent. Definitive treatment is by using chelating agents. There are three chelating agents available: Dimercaprol (British Anti-Lewisite, or BAL), dimercaptosuccinic acid (DMSA, succimer) and unithiol (dimercaptopropane sulfonate, DMPS). BAL is administered in a dose of 3 to 5 mg/kg of deep intramuscular, every four to six hours till the 24-hour urinary arsenic concentration of <50 μg/L.

Q. A 35-year-old man who works in a battery manufacturing unit has come with colicky abdominal pain, constipation, joint pains, decreased libido, and difficulty concentrating. Examination shows impaired short-term memory, anemia, a bluish pigmentation at the gum-tooth line, and bilateral weakness of extensors of ankle and wrist. Discuss about the most likely diagnosis in this patient.

- Diagnosis is acute lead poisoning. Lead exposure can occur in places involved in manufacturing or use of

batteries, pigments, solder, ammunitions, paint, car radiators, cable and wires, and some cosmetics. Leaded fuel was another source of lead exposure, but now lead is not being added to fuels.

- Diagnosis can be confirmed by measuring blood lead levels. Chelation is indicated for individuals with blood lead levels greater than 80 μg/dl. Other useful tests are free erythrocyte protoporphyrin (FEP) or zinc protoporphyrin (ZPP). These two tests measure the effect of lead on hemoglobin synthesis, and can be used as an indicator of lead exposure.
- Chelation should be done by using agents such as DMSA (2,3-dimercaptosuccinic acid, succimer) and calcium EDTA (calcium disodium ethylenediaminetetra-acetate). Recommended dose of DMSA is 10 mg/kg three times per day for five days, followed by 10 mg/kg twice per day for two weeks. Calcium EDTA is administered intravenously or intramuscularly for a three- to five-day period.

Q. A 25-year-old lady presents with history of fever, increased frequency and burning micturition of 2 days duration. Discuss briefly the most likely diagnosis in this patient.

- This patient has urinary tract infection (UTI). Fever, increased frequency and burning micturition are all pointing towards urinary tract infection. Usually females are more likely to get UTI than males because of short urethra (4 cm) and *E. coli* is the common organism causing UTI. More than 5 WBCs in the urine per high power field will confirm the diagnosis of UTI.
- Other helpful investigations in this patient are urine culture and sensitivity. Rarely ultrasound abdomen may be required in cases of recurrent UTI to rule out any urinary tract abnormality.
- A 5-day course of antibiotics should be given to this patient. Antibiotic choices include quinolones (ciprofloxacin or levofloxacin), amoxicillin-clavulinic acid, cotrimoxazole, azithromycin or cephalosporins. Recurrent UTI can be prevented by maintaining good hygiene in the perinial and genitourinary area, passing urine after sexual intercourse. Cranberry juice has been shown to reduce the incidence of UTI by preventing the attachment of *E. coli* fimbriae to urothelium.

Q. A 30-year-old lady has presented with facial puffiness, leg swelling and passing frothy urine. BP is 130/80 mm Hg. Her LFT and RFT reports are normal. Her urine analysis report shows 4+ proteinuria. Discuss the etiology, clinical features, investigations and treatment of the most likely diagnosis in this patient.

- Diagnosis is nephrotic syndrome. Nephrotic syndrome is defined as proteinuria of more than 3.5 gm/day accompanied by hypoalbuminemia, edema, and hyperlipidemia. Normal BP also goes in favor of nephrotic syndrome as hypertension is a feature of nephritic syndrome. Etiology includes minimal change disease (in children), focal segmental glomerulosclerosis (FSGS), membranous nephropathy, diabetes mellitus, SLE and other collagen diseases, amyloidosis, vasculitis, infections (post-streptococcal, hepatitis B, hepatitis C, HIV), and drugs (penicillamine, NSAIDs).
- Other useful investigations are measurement of 24-hour urinary protein excretion, lipid profile and investigations to find out the cause of nephrotic syndrome (such as blood sugar, ANA, cANCA, hepatitis B and C serology, ASO titre, HIV, ELISA, etc.). Renal biopsy is required if the cause is not clear especially in an adult patient.
- *Management*: Edema is managed by dietary salt restriction and diuretics. Hyperlipidemia is treated by dietary modification and statins. Minimal change disease responds to steroids. Membranous nephropathy responds to alternating monthly corticosteroids and monthly oral chlorambucil over 6 months. Membranous nephropathy with progressive renal failure may benefit from cyclophosphamide plus corticosteroids. Underlying cause should also be addressed. Anticoagulation may be required if there is evidence of thrombosis because nephrotic syndrome is a hypercoagulable state due to loss of antithrombin-III in urine.

Q. A 20-year-old boy presents with hematuria, oliguria and generalized edema. His BP is 160/100 mm Hg. His urine analysis shows presence of 1+ poteinuria, WBCs, RBCs and RBC casts. Urea and creatinine are elevated.

- Diagnosis is acute glomerulonephritis. Glomerulonephritis typically presents with hypertension, hematuria, RBC casts, pyuria (WBCs) and mild to moderate proteinuria. Causes of acute glomerulonephritis include primary glomerular diseases (diffuse proliferative glomerulonephritis, focal segmental glomerulosclerosis, membranous glomerulonephritis, crescentic glomerulonephritis, IgA nephropathy), systemic diseases (SLE, Wegener's granulomatosis, polyarteritis, Goodpasture's syndrome), infections (post-streptococcal, syphilis, hepatitis B and C), and serum sickness, etc.
- Treatment usually requires high-dose steroids and cytotoxic agents such as cyclophosphamide. Plasmapheresis can be used in Goodpasture's disease. Underlying disease requires specific treatment.
- Refer 'acute glomerulonephritis' for detailed discussion.

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Q. A 30-year-old man who is a known case of type 1 diabetes mellitus has come to emergency with fatigue, diffuse abdominal pain, vomiting and drowsiness. He was taking insulin daily (total 60 units per day), but has skipped the insulin for the past 4 days. On examination he is tachypneic, has pulse rate of 110 beats per minute, respiratory rate of 28 breaths per minute (deep and sighing type breaths), blood pressure of 100/70 mm Hg. He also has dry mucous membranes, poor skin turgor and is slightly confused. His blood sugar is 450 mg/dl. An ABG done at the bedside shows arterial pH of 6.9, pO_2: 95 mmHg, PCO_2: 28 mm Hg, and HCO of 9 mEq/L. Urine shows presence of large amount of ketone bodies.

Discuss in detail the most likely diagnosis in this patient.

- Diagnosis is diabetic ketoacidosis (DKA). DKA is common in type 1 DM. it is precipitated by acute illness or skipping of insulin. Blood sugar is usually more than 250 mg/dl. Patient presents with fatigue, diffuse abdominal pain due to acidosis and altered sensorium. Patients usually have severe dehydration due to osmotic diuresis caused by hyperglycemia. This patient has dry mucous membranes, poor skin turgor and low normal BP, all of which suggest dehydration. Tachypnea and deep sighing breathing is due to metabolic acidosis. ABG shows metabolic acidosis (low pH and low bicarbonate) and urine shows large amount of ketone bodies confirming the diagnosis of DKA.
- For detailed discussion refer 'DKA' in 'endocrinology and diabetes mellitus' chapter.

Q. A 52-year-old male presents with increasing fatigue and weakness for the past few days. He is a known case of type 2 diabetes mellitus on glimepiride and insulin. He also c/o excessive thirst and passing large amount of urine for the past few days.

Examination shows BP of 70/40 mm Hg; pulse of 115/min; respiratory rate of 22/min; and temperature of 36.9°C. The patient is awake and responsive but disoriented. Mucous membranes are dry and skin turgor is poor. Lab data show blood sugar of 950 mg/dl, and negative ketone bodies in the urine. ABG shows normal pH and normal pO_2 and CO_2.

Discuss the most likely diagnosis in this patient.

- Most likely diagnosis in this patient is hyperglycemic hyperosmolar state (HHS). It is common in type 2 DM. In type 2 DM, there is some residual insulin secretion in the body which prevents formation of ketone bodies. If DKA develops due to ketone bodies, patient become sick and seeks medical attention early. However, in type 2 DM residual insulin prevents ketone body formation and there is rise of blood glucose to very high level (>800 mg/dl) which causes hyperosmolality of blood. Hyperosmolality leads to dehydration of neurons producing altered sensorium and sometimes seizures. Severe hyperglycemia also leads to osmotic diuresis, dehydration and excessive thirst. Low BP and increased pulse rate in this patient are due to dehydration. Another consideration in a patient presenting with hyperglycemia, weakness and dehydration is DKA. But absence of ketone bodies in the urine and normal pH in this patient suggest that it is not DKA.
- For detailed discussion refer 'HHS' in 'endocrinology and diabetes mellitus' chapter.

Q. A 55-year-old man presents with fever, breathlessness, cough with purulent sputum and right-sided chest pain of 3 days duration. Chest pain is sharp, stabbing type and increases on deep breathing and coughing. Examination shows pulse rate of 110/min, respiratory rate of 30/min and BP of 130/80 mm Hg. Chest examination shows crepitations and bronchial breath sounds in right infrascapular area.

Discuss the most likely diagnosis in this patient.

- The most likely diagnosis is lobar pneumonia. Lobar pneumonia usually produces pleuritic type chest pain which this patient has. Bronchopneumonia usually affects both lung and there will be findings in both the lungs which is not the case here. Another consideration is lung abscess, but it presents with significant amount of foul smelling sputum. In addition, pleuritic type chest pain is unusual in lung abscess unless it is closer to the periphery of the lung.
- For detailed discussion refer 'pneumonia' in 'diseases of respiratory system' chapter.

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